THE DESIGN AND INTERPRETATION OF INHALATION STUDIES AND THEIR USE IN RISK ASSESSMENT

ABSTRACTS

March 23-27, 1987
Hannover,
Federal Republic of Germany

ILSI International Life Sciences Institute
Hannover Medical School

Fraunhofer Institute of Toxicology and Aerosol Research

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INBIFO Datum Unterschrift 9. April 87
2484

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CATEGORY A
APPROACHES TO ASSESSING THE TOXICITY OF AIRBORNE TOXICANTS
PAPERS

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STANDARD-SETTING AS AN INTEGRATIVE EXERCISE: ALCHEMY, JUGGLING, OR SCIENCE? - D.V.Bates, University of British Columbia, Vancouver, BC, Canada V6T 1W5

Although there is still controversy over the value of standards to protect the public against harmful exposures, it seems clear that they are needed when some exposure cannot be avoided (such as exposure to common air pollutants), and where high exposures have clearly been responsible for adverse effects. The setting of a standard requires two kinds of integration; the first is the consideration of scientific data from animal exposures, controlled human exposures, and epidemiology; and the second is the balancing of the scientific data with social and political considerations. The whole process, and both types of integration, require simultaneous consideration of 'facts' and 'values'.

The first type of integration is based on the preparation of a 'criteria' document of some kind - essentially a statement and critique of the available scientific evidence; the balance of emphasis in this requires judgements of relevance to any possible standard, as well as a close examination of the consistency, or lack of it, between data derived from the three kinds of information. It is important in this process for there to be appreciation that information can be different in kind; although it may be regarded as being more or less 'scientific', in the sense of being more or less easy to refute, all may be relevant to standard-setting. There is danger in attempting to make an 'a priori' division on the basis of 'relevance' as this may lead to concealment of value judgements on a 'quasi-scientific' basis.

The role of formal risk analysis in this process is limited, and it requires careful definition. A judgement that involves a balance of disparate data, is now regarded by research workers in the field of Artificial Intelligence, as a process requiring the most complex interplay of data analysis; it is a characteristic of the human mind that has not been successfully imitated even by the most complex computer programmes. The total process of standard-setting should be as open as possible, and a clear differentiation between what would be reuired if scientific data alone were considered, and the modification needed on social or political grounds, is a basic requirement for credibility. A major benefit of a structured process is the thorough periodic review of the scientific data base which it requires.

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SPECIES DIFFERENCES IN INHALATION TOXICOLOGY: VARIATIONS IN EXPOSURE-DOSE RELATIONSHIPS AND MACROPHAGE FUNCTION - J.D. Brain, Respiratory Biology Program, Harvard School of Public Health, Boston, MA 02115, U.S.A.

It remains difficult to extrapolate experimental data from one species to another as well as from animals to humans because of interspecies differences. A complete and systematic description of anatomic and functional differences among commonly used laboratory animals in inhalation toxicology is lacking. This paper reviews species differences in relation to aerosol deposition, clearance, and the type and magnitude of biological response to inhaled gases and particles. Different species of animals breathing the same aerosol do not receive identical lung doses, and thus exposure concentration is not an adequate description of lung dose. Parameters that affect the magnitude and distribution of particle retention include differences in ventilation, breathing pattern, collection efficiency, lung anatomy, and clearance mechanisms. Differences in lung macrophage function among laboratory animals will also be emphasized. We have observed significant differences in the rate at which insoluble radioactive gold particles are phagocytized by macrophages of different species in vivo. The rate at which free particles become macrophage-associated is fastest in the Syrian golden hamster and slower in rats and mice. These in vivo differences are not explained by in vitro studies of phagocytic activity of lung macrophages from the same species or by differences in the numbers of macrophages per unit weight or area. Apart from these variations, interspecies differences in substance metabolism and innate biological responsiveness may also influence the extent of lung damage even in cases where lung doses are equal. Further experiments and a comprehensive view of species differences with predictive power is greatly needed.
(Supported by grants HL-31029 and ES-00002 from the National Institutes of Health)

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CELL POPULATIONS OF THE RESPIRATORY SYSTEM: INTERSPECIES DIVERSITY IN COMPOSITION, DISTRIBUTION AND MORPHOLOGY - C.G. Plopper, A. Weir, J. St. George, N. Tyler, A. Mariassy, D. Wilson, S. Nishio, J. Heidsiek and D. Hyde, University of California School of Veterinary Medicine, Davis, CA 95616.

The major site for pulmonary injury resulting from inhaled toxins is the epithelial lining of respiratory airspaces. The extrapolation to humans of inhalation toxicology studies using animal models assumes comparability in tracheobronchial epithelial populations of model species and humans. Using airway microdissection and selective embedding techniques for light and electron microscopy, we have compared the epithelium lining the tracheobronchial airway tree of a number of mammalian species including macaque monkeys, sheep, rabbits and rats. The epithelium of the distal trachea varies between species in the types of secretory cells present and in the abundance of all the cell types present. The bronchioloalveolar junction varies between species in degree of alveolarization, abundance of ciliated and basal cells and in Clara cell ultrastructure. In a single species, the abundance of basal, mucous, Clara and ciliated cells varies between trachea, bronchi and bronchioles. The chemical composition of the stored secretory product of the trachea varies between species from predominantly sulfated to mixed sulfated and acidic to predominantly neutral. The amount of secretory product stored in granules per unit surface area of basal lamina varies in different airway levels in the same species. We conclude that there is a high degree of diversity in tracheobronchial epithelial composition among mammalian species. This diversity includes variation at the same airway level in different species, at different airway levels in the same species, in types of cells present, in abundance of cells present, and in carbohydrate content and amount of stored secretory product.

Supported by grants HL28978, ES00628 and DRR00169.

COMPARATIVE METABOLIC BASIS FOR THE DISPOSITION AND TOXIC EFFECTS OF INHALED MATERIALS - A. R. Dahl, Lovelace Inhalation Toxicology Research Institute, Albuquerque, NM 87185

The inhalation route of exposure is unique in that the inhalant may be substantially metabolized in the nasal cavity or the lungs. The pattern of tissue exposure to both inhalants and metabolites of the inhalants may be considerably different than when the same substance is administered by any other route. For example, inhalant metabolites formed in the nasal cavity subsequently may be swallowed, thus exposing the alimentary tract to potential toxicants. On the other hand, metabolites formed in the lung may be cleared via the blood, thus exposing the heart to relatively nigh concentrations of metabolic products. Knowledge of the rates of respiratory tract metabolism for different inhalants, the site of metabolism (i.e. nasal or pulmonary), the products of such metabolism, the fate of metabolites produced in the respiratory tract, the effects of concentration or coadministration of a second inhalant, and differences in respiratory tract metabolic capability among animal species indicates that such metabolism may indeed be important in determining the toxic effects of inhalants. For example, knowledge of the nasal metabolism of hexamethylphosphoramide (HMPA) in rats and benzo(a)pyrene (BaP) in Syrian hamsters has been used to explain the carcinogenicity of these compounds when inhaled; and, demonstrated differences in the lung tissue metabolism of butadiene among animal species, including man, is proving useful in extrapolating animal toxicity data to man. [Research performed under U.S. Department of Energy Contract No. DE-AC04-76EV01013.]

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AN INTEGRATED SCREENING METHOD FOR EVALUATING THE TOXICITY OF INHALED PARTICULATES: VALIDATION OF THE METHOD - DB Warheit, Du Pont-Haskell Lab, Newark, DE, USA.

There is a great need for the development of a rapid and reliable bioassay to evaluate the toxicity of inhaled particles. A number of methods have been proposed- including clearance studies, lavage analyses and in vitro cytotoxicity tests. These methods are often limited in scope inasmuch as they measure only one dimension of the pulmonary response to inhaled, instilled or incubated dusts. Accordingly, a comprehensive approach to lung toxicity studies has been developed. The method has been validated by exposing rats either to silica (Si-alpha quartz) or carbonyl iron (CI) particles. Rats were exposed to aerosols (100 mg/m^3) of Si or CI for 3 or 6 hrs or 3 days. Recovery periods included 0, 24, 48 hrs, 8 days, 1,2, and 3 months postexposure. The lungs from one group of sham and dust-exposed rats was lavaged. After centrifugation, the supernatant was measured for protein and LDH. The cell pellet was counted and measured for viability, differential and cytochemical analyses. Subsequently, these cells, primarily pulmonary macrophages (PM), were cultured and studied for morphology and in vivo phagocytosis by scanning electron microscopy (SEM). Additional PM were cultured for in vitro chemotaxis and phagocytosis. Another group of sham and dust-exposed rats was subdivided into two groups. Group A was perfusion-fixed through the vasculature for lung digestion-clearance studies. Group B was airway fixed for histopathology (LM), SEM and TEM, where particle deposition and translocation to interstitium or lymph nodes, early cellular responses, and in situ chemotactic and phagocytic responses by alveolar and airway macrophages were evaluated. Our results showed that although particle deposition patterns for the 2 dusts were identical, brief doses of Si elicited a permanent inflammatory response (PMN) concomitant with increases in LDH and proteins in the lavage ($p<0.01$) PM functional capacity was depressed ($p<0.05$). Inflammatory lesions could be observed by histopathology within 1 month after exposure. In contrast, 6 hr or 3 day exposure to CI produced no cellular, cytotoxic or permeability changes at any time postexposure. PM function was either enhanced or unchanged from controls. Evidence supports the conclusion that silica is substantially more toxic to the lungs than CI and serves to validate this method as a reliable bioassay for evaluating the lung toxicity of inhaled materials.

A MULTIDIMENSIONAL APPROACH TO THE CHARACTERIZATION OF ACID AEROSOLS FOR HEALTH EFFECTS - C.A.Franklin and B.Stern, Environmental Health Directorate, Department of National Health and Welfare, Ottawa, Canada K1A 0L2.

To assess the toxicity of long range transported air pollution and its potential adverse effects on human health, the description and characterization of the transformation products (e.g. H_2SO_4, NH_4HSO_4, and $(NH_4)_2SO_4$) that comprise a major portion of the pollutant mixture are essential. In a multiphase study we first developed a model detailing some mechanistic hypotheses for the action of acid particulates on the tracheobronchial region of the human lung. It was used to calculate the size range of an acidic particle, large enough to carry sufficent acid to deliver a localized irritant pulse and small enough to penetrate to the tracheobronchial region where epithelial tissue is relatively unprotected by the mucus layer. The mass median aerodynamic diameter (MMAD) of such a particle was estimated to be in the range of 0.5 to 2.0 microns, taking into consideration the deposition efficiency of particles, the diameter of the airways, the acid content of the incoming particles per unit weight, and the effect of neutralization by ammonia in the upper respiratory tract. Second, the size distribution of acid particles during long-range transport events in southwestern Ontario in the summer of 1986 was monitored, using two modified multi-stage cascade impactors that were run concurrently. The impactors had a cutoff diameter for each of their six stages of 5.0, 2.6, 1.0, 0.6, 0.2 and 0.1 um, respectively. One of the impactors was connected to a humidifying system which allowed for hygroscopic growth of particles, to simulate conditions in the upper respiratory airways. Preliminary data indicate that over 90% of the acid fraction was present in particles less than 1 micron MMAD. The data generated from the theoretical model and from environmental monitoring permit a more precise and biologically relevant characterization of ambient acid aerosols which is essential for the design and interpretation of critical studies in air pollution epidemiology and animal toxicology.

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CELLULAR APPROACHES TO ASSESS THE TOXICITY OF AIRBORNE TOXICANTS ON AIRWAY EPITHELIAL PATHOPHYSIOLOGY.

George Leikauf, University of Cincinnati, Cincinnati, OH 45267-0182

The airway epithelial cell has a unique role in pulmonary defense. The epithelial cell "sees" inhaled toxicants first and in the highest concentrations. To defend the airways, this cell is equipped with various barrier and secretory capabilities (including ion transport, with passive water movement, and mucus secretion), which enact dilution, formation of protective barriers, and removal of inhaled pollutants through mucocilliary clearance. Detailed elevation of these functions and the underlying cellular regulatory mechanisms would be aided greatly by the employment of in vitro cell systems. To examine the effects of inhaled toxicants on the airway epithelium, cells from bovine trachea were isolated (2% dispase, 5mM dithiothreitol) and grown to confluency on collagen-coated dishes. The resulting cell monolayers were examined employing light, transmission, and scanning electron microscopy. Cells in culture retained a distinct membrane polarity characteristic of epithelial cells. The apical membranes were covered with short microvilli, coated with a glycocalyx, and occasional cilia. These membranes were clearly distinguished from the basolateral membranes which consisted of smooth, interdigitating processes. Cells in culture developed distinct junctional complexes containing desomosomal structures and membrane fusions (tight junctions). Within each cell, extensive networks of keratin microfilaments were observed by electron and indirect immunohistological epifluorescent microscopy. Cell monolayers were exposed to ozone in vitro using specially designed exposure chambers containing rotating, inclined platforms. Following exposure, the release rates of various arachidonic acid metabolites were assessed, and ozone induced unique arrays of cyclooxygenase and lipoxygenase products depending on the exposure concentration. These studies clearly demonstrate the feasibility of employing newly-developed in vitro cell culture methods to assess the pathophysiologic effects of airborne toxicants on the airway epithelium.

IN VITRO / EX VIVO INVESTIGATIONS ON THE EFFECTS OF CARCINOGENS AND POTENTIAL LUNG IRRITANTS TO LUNG AND LIVER CELLS

– B.L. Pool , P. Aulenbacher*, R.G. Klein, P. Schmezer, and W.J. Zeller, Institute for Toxicology and Chemotherapy, German Cancer Research Center, and * Thorax Clinic Rohrbach, 6000 Heidelberg, F.R.G.

The influence of common air pollutants on the induction of cancers by environmental carcinogens has not been studied sufficiently to date. Therefore a collaborative study has been initiated to assess the toxic, genotoxic and carcinogenic effects of air contaminants (SO_2, NO_x, Benzo(a)pyrene and N-Nitrosodimethylamine) alone and in combination using in vitro and in vivo methods. For this, the local and systemic effects of various air pollutants is being investigated in a longterm carcinogenicity assay in the rat. In analogy to this bioassay, cells are being explanted after in vivo pretreatment with SO_2/NO_x alone or in combination with the carcinogens and are being subsequently assayed in vitro for cytotoxicity and genotoxicity, as well as for their capacity to metabolize carcinogens to bacterial mutagens. These studies are directed toward the elucidation of additional local and systemic biological effects, which may be caused by the compounds. In vitro, human lung cells (to assess the susceptibility of the relevant species) and fetal hamster lung cells (to assess the susceptibility of the repiratory system in early developmental phases) are being assessed for toxic and genotoxic effects induced by the air pollutants, alone and in combination.

So far following effects have been observed:

1. In vivo application of SO_2 does not systemically affect the in vitro generation of toxic or genotoxic effects of N-Nitrosodimethylamine, or the toxic effects of Benzo(a)pyren to liver cells.
2. SO_2 and NO_x, alone or in combination are toxic to fetal lung cells, when determining the plating efficiency, but not when the exclusion of trypan blue is taken as the parameter of toxicity. The additional effects on genotoxicity are being elucidated.
3. Human lung cells are capable of metabolizing N-Nitrosodimethylamine and N-Nitrosomethylbenzylamine to genotoxic intermediates. Therefore, they may be used to study the influence of SO_2/NO_x on the induction of genotoxic events induced by these compounds.

In conjunction to the ongoing longterm bioassay, these and future results are anticipated to yield a reasonable data base for estimating human risk according to the parallellogram approach.

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CYTOTOXIC, MUTAGENIC AND CARCINOGENIC EFFECTS OF AIRBORNE PARTICULATES ON HUMAN AND RODENT TISSUE CULTURE CELLS: A COMPARATIVE STUDY FROM A HIGHLY INDUSTRIALIZED AREA OVER A PERIOD OF 11 YEARS (1975 - 1986) - N.H.Seemayer, W.Hadnagy, R. Tomingas and N.Manojlovic, Medizinisches Institut für Umwelthygiene an der Universität, Gurlittstr. 53, D-4000 Düsseldorf, F.R.G.

Epidemiological studies reveal a higher incidence of lung cancer in industrialized regions. Air pollutants, especially airborne particulate matter which contains more than 500 various chemical substances are supposed to be responsible for this phenomenon.
Samples of airborne particulate matter were collected at various places of the heavily industrialized Rhine-Ruhr area (F.R.G.) between 1975 and 1986. Extracts and fractions of airborne particulate matter were prepared with organic solvents and quantitatively transferred to dimethyl sulfoxide.
We report about cytotoxic, mutagenic and carcinogenic effects of extracts and fractions of airborne particulates on human and rodent tissue culture cells.
Cytotoxicity is evaluated by loss of cell viability of human and rodent macrophages and by reduction of "plating efficiency" of human and rodent lung cell lines in vitro. Mutagenicity is shown by induction of "sister chromatid exchanges" in human lymphocyte cultures and Chinese hamster lung cell line V 79. Furthermore, "point mutations" at the HGPRT-gene locus of V 79 cells are presented. Carcinogenicity is demonstrated by "enhancement" of malignant cell transformation of Syrian hamster kidney cultures, infected with Simian virus (SV-)40.
We present data on dose-effect relationship of various samples of airborne particulates and discuss aspects of risk evaluation.

BIOCHEMICAL AND FLOW CYTOMETRIC ANALYSES FOR THE EVALUATION OF INHALATIVE HAZARDS:
LONG-TERM EXPOSURE TO CADMIUM AEROSOLS

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To improve the feasibility and evidence of toxicological and genotoxicological studies in rats continuously exposed to CdO, CdS and combinations of CdO and ZnO aerosols we used biochemical analyses and flow cytometric measurements of lungs cells. The bioavailabitity of these water insoluble compounds was determined by AAS-analyses of various tissues. Analyses of lung lavage showed informations on the cytotoxic action of the inhaled aerosols, but also increased abundances of alvealar macrophages and enhanced proliferation rates of the lung cells detected as increased fractions of S-phase cells.
The accessory lobes of the lungs were used for flow cytometric measurements. It was found that inhalation of Cd containing aerosols resulted in an increased variability of the nuclear DNA content indicating a genotoxic action of the treatment.
This induced variability of the cellular DNA content was significantly increased already after 3 months of exposure to 30 $\mu g/m^3$ Cd as CdO. The strongest effect was found after 18 months of exposure to 90 $\mu g/m^3$ Cd as CdS.
Combined CdO and ZnO exposures were shown to be antagonistic.

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BENZO(A)PYRENE-7,8-DIOL-9,10-EPOXIDE(BPDE)-DNA-ADDUCTS AND MONO-OXYGENASE ACTIVITIES IN MICE TREATED WITH CIGARETTE SMOKE(CS) OR BENZO(A)PYRENE(BP) IN VIVO - N.M. Bjelogrlic, M.Iscan, O.Pelkonen and K.Vähäkangas, Department of Pharmacology, University of Oulu, SF-90220 Oulu, Finland.

CS contains e.g. BP, which is carcinogenic to animals. The carcinogenic activity is generally thought to be due to metabolic activation of BP by mono-oxygenase and epoxide hydrolase to BPDE which then binds covalently to guanine in DNA. We have studied the formation of BPDE-DNA-adducts and mono-oxygenase activities in vivo in mouse after CS and BP exposure. Mice(C57BL/6) were exposed to CS for 3, 5 or 16 days in a chamber where smoke and fresh air were lead alternatively. Another group of mice was injected i.p. by BP(4-80mg/kg). BPDE-DNA-adducts in lung and liver DNA were analyzed by synchronous fluorescence spectrophotometry(1). Mono-oxygenase activities were measured in tissue homogenates. The level of BPDE-DNA-adducts was below the limit of the assay (10fmol/100ug DNA) in both tissues studied after CS exposure even though aryl hydrocarbon hydroxylase (AHH) was induced about 25-fold in lung after 3 days exposure and 7-ethoxyresorufin O-deethylase (ERDE) about 2-fold in liver after 3 and 5 days exposure. The lowest dose of BP needed to get detectable levels of BPDE-DNA-adducts in both tissues was 20mg/kg. AHH was clearly induced in lung after BP exposure but less than with CS exposure. In liver AHH-activity was increased only by BP. ERDE was maximally induced in both tissues even with the lowest doses of BP used. Thus, AHH-activity may not be a good indicator for the relevant activation pathway of BP.

1. Vähäkangas et al., Carcinogenesis 6:1109, 1985.

ACUTE BRONCHIOLAR DAMAGE OF BROMOBENZENE INHALATION IN MICE AND RATS - J.E. Dahl, K. Aarstad, O. Nilsen and E. Dybing. Department of Toxicology, National Institute of Public Health, Oslo, and Department of Pharmacology and Toxicology, University of Trondheim, Trondheim, Norway.

Bromobenzene, a well known hepatotoxin, has also been found to produce bronchiolar Clara cell injury in mice after intraperitoneal or oral administration (Reid et al., 1973; Forkert, 1985). In the present study, the bronchiolar effects of bromobenzene inhalation were investigated in mice and rats.

Sprague Dawley rats and C57BL/6 mice were exposed to 0, 250, and 1000 ppm of bromobenzene for 4 hr and killed 2 days after termination of exposure. By inserting a cannula in the truncus pulmonalis through an incision of the right cardial ventricle, the lungs were perfused by buffered saline followed by glutaraldehyde fixative. Blocks of 1 mm^3 were taken from the lungs and embedded in Vestopal W. Sections were cut and stained with methylene blue-azure II-basic fuchsin and double stained with uranyl acetate and lead citrate for light microscopic and transmission electron microscopic studies, respectively.

In the mice exposed to 250 ppm of bromobenzene, the bronchiolar Clara cells demonstrated extensive cytoplasmic vacuolization and, to some degree, exfoliation. In contrast, the ciliated cells appeared as in control animals. Injury to the entire brochiolar epithelial lining was observed in mice exposed to 1000 ppm bromobenzene. The ciliated cells were highly vacuolated and necrotic changes had taken place in the Clara cells. No bronchiolar effects of bromobenzene inhalation were evident in rats. Thus, in mice, inhalation exposure to bromobenzene caused acute bronchiolar injury comparable to that seen after intraperitoneal or oral administration.

This study was supported by The Royal Norwegian Council for Scientific and Industrial Research.

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Datum, Unterschrift 9. Apr. 87

SOLUBILITY STUDIES ON AN INDUSTRIAL PLUTONIUM DUST -

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The 'solubility' of mixed plutonium/uranium oxide fuels determines the validity of urine monitoring in assessing systemic burdens and intakes. In-vitro studies of long term 'solubility' over periods comparable with the residence time in the lungs was the objective of this project. The magnitudes of, and variations in, solubility with time for a particular fuel dust have been studied for over two years using laboratory rigs simulating the human lung under carefully controlled conditions. These studies did not attempt to investigate any other removal mechanisms. The lung assemblies consist of a semi-permeable membrane containing the fuel and lung fluid mixture. This is swept by blood simulant at constant 1.5 litres/day flow rate. Considerable efforts to describe the pore size and behaviour of the membrane were undertaken at the beginning of the experiment.

Three experimental assemblies have been run in parallel. One of the assemblies contained transferrin in its blood simulant. Disolution data is compared for all three assemblies for plutonium-239, uranium and americium-241. Interesting early conclusions are that americium removal is similar in all assemblies and that uranium transport exhibits a short half-life at about 2 to 5 days.

ANALYSIS OF PHOSPHOLIPID/APOPROTEIN RATIO IN EXTRACELLULAR SURFACTANT AFTER EXPOSURE TO NITROGEN DIOXIDE OR A METHYL FURAN DERIVATIVE - F. Lawrence and K. Miller, British Industrial Biological Research Association, Carshalton, Surrey, SM5 4DS, U.K.

Whereas it is well known that the surfactant system relies on the correct balance of constituent phospholipids to maintain functional surfactant on the alveolar surface, the physiological role of the protein found in surfactant has not been elucidated. Equally, little is known of the relevant mechanisms regulating the system. Analysis of phospholipid/apoprotein ratios in extracellular surfactant after exposure to toxic insult may therefore be of importance in determining these mechanisms. Extracellular surfactant recovered from hamsters exposed to either nitrogen dioxide (NO_2) or 3-hydroxymethylfuran-N-ethyl carbamate (HFC) has shown raised levels of phospholipid compared to control animals but the composition of the phospholipids has remained essentially unchanged. We report here the development of a specific ELISA assay for the hamster apoprotein(s) and the analysis of phospholipid/apoprotein ratios in surfactant from animals exposed to the above toxic agents.

An antiserum to hamster extracellular surfactant was raised in rabbits and the Ig fraction purified by absorption of anti-serum activity using affinity chromatography against a CNBr-Sepharose column linked to hamster serum proteins. Hamster surfactant was serially diluted for adsorption onto ELISA plates and probed for with a fixed concentration of the purified antibody. Animals were exposed to either 15ppm NO_2 for 24 hrs and lavaged immediately or given an i/v dose of 20mg/kg body weight of 3-HFC and lavaged after 48 hrs. NO_2 caused an increase of around 100% in the level of apoprotein recovered while 3-HFC gave an increase of around 200%. Both these results are consistent with the increases found in the phospholipid levels after similar exposures and support the view that NO_2 and HFC act on the surfactant system by altering the control of the secretion, recycling or catabolism rather than by disturbing the synthesis of lipids or proteins directly concerned with functional surfactant. Since NO_2 and HFC both cause specific injury to the Clara cell in hamsters it may be implied that in this species the Clara cell could be involved in the control of the surfactant system.

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CYTO- AND GENOTOXIC EFFECTS OF AUTOMOBILE EXHAUST ON MAMMALIAN CELLS IN VITRO - W.Hadnagy and N.H.Seemayer, Medical Institute of Environmental Hygiene at the University, Düsseldorf, FRG

Ambient air, mainly of urban and industrial areas, contains a large number of chemical substances including mutagens/carcinogens. It is known, that the main part of mutagens/carcinogens originates from various combustion sources as power plants, residential heating and also from automobile traffic. We analysed the extract of particulate matter (EPM) from gasoline engine exhaust for cytotoxic and genotoxic properties using mammalian cell cultures. In presence of EPM, no considerable loss of cell viability of mouse macrophages of cell line IC-21 and of Chinese hamster lung cells V79 was observed. On the contrary, using the same EPM concentrations, a strong dose-dependent reduction of plating efficiency was found utilizing three different cell lines (Syrian hamster kidney cells 14-1b, human lung cell line A 549 and V79 cells). The latter effect was found to be caused by a strong increase of so-called C-type mitoses revealing mitotic arrest. The mitotic index of about 2% from control values raised up to 14.6% for IC-21 cells and 38.4% for V79 cells. As a consequence of this effect on cells in mitosis, EPM led to aneuploidy and polyploidy in V79 cells in a dose-dependent manner. Our results suggest, that automobile exhaust from gasoline-powered engines contains highly reactive substances which impair reproductive capacity of mammalian cells by mitotic arrest leading to the cytogenetic endpoint of aneuploidy and polyploidy which may be associated with cancer development.

URINARY METABOLITE PROFILES AND PHARMACOKINETICS OF ANTIPYRINE IN SMOKERS AND IN EX-SMOKERS
R. SCHÜPPEL, H. BÄSSMANN - Inst. Pharmakol. & Toxikol., Techn. Univ. Braunschweig, FRG

Due to inductive effects of smoke constituents on hepatic cytochrome-P-450-isoenzymes, the disposition of a number of drugs is found to be accelerated in cigarette smokers. In order to analyse these inductive effects, the disposition of the model drug antipyrine has been assessed in heavy smokers by determining the complete urinary metabolite profile of the drug along with its pharmacokinetics from saliva.
Urinary output of 12 phase-I and -II metabolites and unchanged antipyrine was measured over 48 h after a standard oral dose of 1200 mg antipyrine. Elimination kinetics of antipyrine was followed in saliva samples up to 56 h after dosing.
Only small, but statistically highly significant changes were observed in the urinary profiles for some metabolites in smokers, compared to a control group indicating a discreet derangement of the activity or specificity of phase-I and/or phase-II reactions involved. However, pharmacokinetic parameters, derived from saliva samples, e.g. total metabolic clearance or half-life time exhibited clear and significant differences, as expected.
In a second series, pharmacokinetics of antipyrine has been followed in a group of ex-smokers (n=13) for up to 11 month after quitting, in order to assess the time course of normalization, if any, of pharmacokinetic parameters of the drug. No information is yet available as to the persistence of inductive effects of sustained, inhalatory smoking. Tests were performed sequentiually about 4 weeks apart for each participant.
As judged by either half-life time or total clearance values, there is no prompt normalization of pharmacokinetic parameters of antipyrine after quitting. Only part of the volunteers studied exhibit a trend for normalization at all, which becomes recognizable after 6-9 month. the rest remains without clear-cut changes for up to 11 month. When the study was terminated. Results show, that induction of mixed-function oxidase in smokers exhibits marked persistence, not recognized as yet.

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INBIFO Datum, Unterschrift 9.04.87 Ra

FACTORS CONTROLING PARTICLE ELIMINATION AND PENETRATION IN THE LUNG: EFFECTS OF DUST PROPERTIES

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The specific harmfullness for instance fibrogenicity or cancerogenicity of dusts from various working places is based on the dust deposited and stored in the lung parenchyma. Inhalation experiments were designed with the aim of estimating the range of factors controling dust elimination from the lung under conditions of occupational dust exposure. It was found that dusts from the mining industry develop an approximately threefold variability of the elimination rate in dependancy from the mineralogical composition and the cytotoxicity. Other effective factors were the particle size distribution of the dust. The role of the cytotoxicity in vitro of dust in the pathogenicity of pneumoconioses is discussed.

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CATEGORY B
METHODOLOGICAL ISSUES IN DESIGNING AND CONDUCTING STUDIES WITH LABORATORY ANIMALS
PAPERS

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2484
Bestätigung der Übereinstimmung mit dem Original
Datum, Unterschrift 2.Apr.87

EXPOSURE FACILITIES AND AEROSOL GENERATION AND CHARACTERIZATION FOR INHALATION EXPERIMENTS

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In order to assess the risk involved in using materials or processes releasing aerosols, it may be necessary to perform experiments under well controlled conditions.

Depending on the problem, a wide variety of different designs from whole body to nose only exposure facilites have been described in the literature. Depending on the animals' demands on temperature, humidity, O_2 levels the ventilation rate has to be adjusted while simultaneously the requirement of aerosol homogeneity even for different particle sizes has to be met. Design criteria are presented and the actual performance of different designs is discussed.

Stable aerosol generation with respect to concentration and size distribution is of key importance to the quality of the study. Different methods laboratory generation (liquid atomization, dry redispersion, condensation, radioactive labeling) as well as reliable production from combustion sources (Diesel, coke oven etc.) will be presented with examples.

The deposition of particles in the nasopharyngeal, broncheal and alveolar tracts are determined to a large extent by the physical properties of the aerosol, while the effects of the deposited material are thought to depend on the mass. For these reasons, the aerosol has to be characterized. Different methods mainly with emphasis on the direct determination of mass will be discussed. In view of GLP conditions the importance of on line computer controlled aerosol generation and characterization will be illustrated by examples.

COMPARISON AND INTERPRETATIONS OF DIFFERENT METHODS USED IN ACUTE AND SUBCHRONIC INHALATION STUDIES WITH POTENTIAL LUNG IRRITANTS WITH PARTICULAR ATTENTION TO PULMONARY FUNCTION - MEASUREMENTS

J. PAULUHN, BAYER AG, Wuppertal-Elberfeld.

The inhalation toxicity of a non-volatile liquid has to be investigated as an aerosol. High aerosol concentrations may be generated by nebulizing these substances with or without an appropriate solvent or carrier and should be of maximum respirability for the animal species used. The atmosphere should be characterized as accurate as possible with regard to the size distribution of particles and actual concentration in the vicinity of the breathing zone of the animals. The results using different analytical procedures and equipment i.e. gravimetric and chromatographic techniques, the BERNER-cascade-impactor and the TSI-APS 33 Laser-Velocimeter are compared with particular attention being payed to sampling efficiency, wall-losses, anisokinetic sampling biases and the calculation of number and mass related aerosol distribution-parameters. All the results show that the conformity of all analytical data is good when the basic requirements of aerosol physics are observed.

The effectiveness of a new exposure system is discussed in context with the results of acute and subchronic isocyanurate (Desmodur N 3300®) inhalation studies. It has been demonstrated that the results of lung function measurements (lung mechanics, lung volumes, flow-volume-time relationship, acetylcholine-provocation test) agree both with an altered body-weight - lung weight ratio and the histomorphological investigations. These studies revealed that there was a clear threshold for lung damage independent of the type of the study (acute, subacute, subchronic inhalation).

The applicability and diagnostic value of the above mentioned lung function parameters have been demonstrated in routine inhalation toxicity studies with deep and upper respiratory tract irritants using small number of animals (rats).

All lung function measurements revealed that this technique is as sensitive as other sensitive post mortem evaluations performed in inhalation toxicity studies. But as this technique can be performed repeatedly in a non-invasive manner it provides a deeper qualitative and quantitative insight into toxic effects on the lung without sacrificing the animal.

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CHRONIC TOXICITY INHALATION STUDIES: PROTOCOLS AND PITFALLS - P.E. Morrow and R. Mermelstein*, University of Rochester and Xerox Corporation*, Rochester, NY USA

Chronic toxicity testing by the inhalation route is probably the most difficult to design, perform and interpret of all testing routes. The development of protocols for chronic inhalation studies (2-year) depends upon pre-chronic study findings. Otherwise, sparse guidance is available to the investigator who must choose exposure levels that are both suitable for the needs of regulatory agencies e.g., revealing carcinogenic effects, while meeting the criteria of the inhalation toxicologist and pathologist in matters of dosimetry and interpretability of effects. This presentation considers many important issues in the chronic exposure design and then describes, in considerable detail, a strategy for setting chronic exposure levels which minimizes the probability of overloading the lungs by the use of pre-chronic study findings and appropriate respiratory models. Evidence is presented that excessive lung particulate levels lead to a compromise of normal host defense mechanisms in the lungs, especially the ability of the pulmonary macrophage to translocate particulate toxicants out of the respiratory system. In turn, this condition appears to lead to lung injury of a non-specific nature. Excessive dust levels in the lungs not only cause an alteration in the retention and disposition of dust within the lungs, but are associated with the development of fibrogenicity and tumorigenicity, even when the dusts are generally regarded as innocuous.

CARCINOGENICITY PROTOCOLS* - R. A. Griesemer, Oak Ridge National Laboratory, Oak Ridge, TN 37831.

Carcinogenicity protocols for respiratory routes of exposure do not differ in principle from those for other exposure routes. In practice, however, inhalation bioassays in animals require special attention to exposure monitoring and to chamber-related alterations in respiratory function. The temptations to reduce costs through smaller group sizes, mixing of sexes in the same chamber, fewer concentrating levels, early sacrifice intervals, or deletion of chamber-control groups must be avoided.

Because inhalation bioassays are cumbersome and expensive, few substances have been tested adequately by this means in spite of the importance of the respiratory tract as a target site and as a portal of entry for environmental chemicals. Alternate exposure modes that have been developed include direct injections into the lung parenchyma, the pleural or mediastinal cavities, or into the bronchial mucosa; intratracheal injections; repeated topical applications to localized sites by lavage or into heterotransplanted tracheas; and systemic administration. The most commonly used model systems for respiratory carcinogenicity assays are intratracheal instillations in Syrian hamsters and intratracheal or parenteral administration to strain A mice. The significance of induction of excess lung tumors in strain A mice that have a high spontaneous background is analogous to that of induction of liver tumors in some C3H strains and skin tumors in SENCAR mice, yet is perceived differently by some investigators.

Efforts to develop short-term in vivo assays based on biochemical markers of early foci or two-stage protocols have lagged behind the progress in other organ systems. Prospects for in vivo/in vitro assays are promising but require validation.

*Research sponsored by the Office of Health and Environmental Research, U.S. Department of Energy under contract DE-AC05-84OR21400 with the Martin Marietta Energy Systems, Inc.

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Bestätigung der Übereinstimmung mit dem Original
Datum, Unterschrift 9.Apr.87
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Source: https://www.industrydocuments.ucsf.edu/docs/fmhl0000

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Bestätigung der Übereinstimmung mit dem Original
Datum, Unterschrift 9.4.87

THE INTERACTION BETWEEN AIRBORNE POLLUTION AND RESPIRATORY INFECTION: SURVIVAL OF AN AIRBORNE PATHOGEN, Escherichia coli - C.M.Wathes and K.Howard, Department of Animal Husbandry, University of Bristol, Langford, Bristol BS18 7DU,U.K.

Chronic exposure to airborne pollutants can render animals more susceptible to infection by respiratory and other pathogens. A microorganism is subjected to many physical and biochemical stresses when it is dispersed into the atmosphere, while it remains airborne, and following inhalation. Whether or not infection proceeds to disease depends on the fate of the microorganism after inhalation which, in turn, is determined by the infective dose and the animal's immune status.

We have used a modified Henderson apparatus to examine the influence of the culture medium and the composition of the suspension fluid on the airborne survival of Escherichia coli at different temperatures and humidities. Physical losses within the apparatus were assessed either by radiolabelling the bacteria during growth with tritiated thymidine or methionine or by adding a spore tracer, Bacillus subtilis, var. niger.

E.coli proved to be a robust microorganism in air. Death occurred in two phases, the first lasting approximately 1 minute; in the second the number of viable micro-organisms declined exponentially. Death was most rapid at low humidities (50% rh) at 15 and 30°C, with half-lives of 14 and 3 minutes respectively. In humid conditions the half-lives were much longer, approximately 83 and 14 minutes respectively. The survival of E.coli suspended in an artificial simulant of a diarrhoeic faecal slurry was similar to that of E.coli in distilled water.

The viability, and presumably also the infectivity, of an airborne microorganism is affected by the culture conditions, the method of aerosol generation and climate. These factors should therefore be controlled when aerosolised pathogens are used in studies of inhalation toxicology.

AN INVESTIGATION OF LIMITATATIONS OF A CONTROLLED VAPOUR GENERATION SYSTEM - R.B. Douglas, London School of Hygiene and Tropical Medicine. London, WC1E 7HT.

During the development of a system using a bubbler (a thermostated Dreschel bottle) at different flows and a variety of dilutions it became apparent that there were discrepancies between the theoretical concentrations based upon saturated vapour pressure (trilene) and actual values as measured by batch calibrated gas detector tubes. A subsidiary experiment in which a thermostated light polythene bottle was weighed before and after a period at constant flow confirmed that saturation of a bubbled airflow may be less than 100%. Records of flows and concentrations for the main system were re-examined and analysed. Firstly, plotting theoretical value against estimated reading (gas detector tube) showed a correlation of r = 0.79. This was followed by plotting absolute discrepancies against bubbler flow (r = 0.85). Next, a flow dependent fractional saturation "F" was defined theoretically and estimated as the ratio of detector tube to nominal reading. Over a wide range of values of "F" (0.95 - 0.24) a close linear relationship was found with flow (r = 0.98) thus finally allowing calculation of corrected values. The system was further modified by the addition of a condensing chain.

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Datum, Unterschrift 9.Mai 87

DESIGN AND EXPERIENCE WITH HEAD/NOSE-EXPOSURE TECHNIQUES IN A 2-YEAR INHALATION STUDY WITH RATS

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BASF Aktiengesellschaft, Department of Toxicology

The increasing use of head/nose exposure techniques for aerosol inhalation studies has made further development necessary. Modular head/nose exposure systems were constructed of glass/steel with glass or plastic tubes for the exposure of 20 -120 rats. The design of the tubes was optimized to avoid unacceptable effects on the animals (heat build-up; stress by firm restrainment). Concentration profiles of aerosols were measured at different positions inside the tubes to define the influence on dosage if the animals move in the tubes. In a 2-year study 50 Fischer 344-rats per sex and group were exposed to air 6 h/d on 5 d/w: one group was head/nose exposed (glass tubes), another group was exposed in whole body inhalation chambers. Room housed rats were taken as controls. Satellite groups of 10 rats per sex and group were exposed for 3, 6 and 12 months for clinico-chemical analysis, hematology and urinalysis. Results: Body weight of the head/nose exposed rats compared with the chamber exposed and room housed groups was significantly lower after about 1-month exposure and remained retarded until the end of exposure. There were no indications that other parameters were changed. In a subsequent test the influence of different tube materials (glass or plastic) and age of the rats (45 and 110 days old) on body weight gain was examined. Different tube materials and tube design showed the same effect of body weight retardation. Determinations of thyroxine (T3) and trijodothyronine (T4) levels revealed no indications of an influence on the thyroid system. In a 1-month post-exposure period which followed head/nose exposure exposed for 2 months younger rats showed a better adaptation of the body weight to that of chamber exposed rats than older rats.

Increased efficiency of animal use in acute inhalation toxicity experiments to determine the LC50 rat at different exposure periods.

W.F. ten Berge and A. Zwart
DSM, Geleen, NL CIVO-TNO, Zeist, NL

The influence of the number of animals per trial on the variation coefficient of the LC50 was studied by use of Monte Carlo simulation of the ammonia study, published by Appelman et al. (1982).

In this study 200 rats were used to determine the LC50 of ammonia for 10, 20, 40 and 60 minutes. This quantity of rats corresponds well with the generally accepted number of 50 rats per LC50 value. In the Monte Carlo simulation of the ammonia study the number of rats per trial was varied from 10 to 1. For each set of independent variables (concentration, time, sex) and for each number of animals per trial 500 simulations were performed. The variations coefficient of the simulated LC50 values increased from 2% to 4% when decreasing the number of rats per trial from 10 to 5. A further increase in the variation coefficient to 10% was observed, when the number of rats per trial decreased to 1. The results of the Monte Carlo simulation show, that using 50 animals in a well designed experiment allows the determination of the acute inhalatory LC50 at 4 different exposure periods with sufficiently narrow 95% confidence limits.

The condition to achieve this in practice is to choose exposure concentrations and exposure periods in geometric progression, to use one or two animals per trial and to analyse the raw data by the method of Maximum Likelihood according to Finney (1977). This method is comparable to a weighted multiple regression analysis, in which concentration, exposure period and sex are independent variables, controlling the mortality response.

Reference:

Appelman, L.M., W.F. ten Berge and P.G.J. Reuzel, 1982.
Acute inhalation toxicity study of ammonia in rats with variable exposure periods.
American Industrial Hygiene Association Journal 43, 662-665

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Source: https://www.industrydocuments.ucsf.edu/docs/fmhl0000

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Bestätigung der Übereinstimmung mit dem Original
Datum, Unterschrift 9.Apr.87

ACUTE INHALATION TOXICITY OF A PRESSURISED AEROSOL HOUSE HOLD INSECTICIDE FORMULATIONS

- M.V. Moorthy and A. Seshaiah, Department of Toxicology, Fredrick Institute of Plant Protection and Toxicology (FIPPAT), Padappai 601 301, India.

In India, only few laboratories have facilities for studying inhalation toxicity of technical grade, liquid, wettable powder and dust formulations of pesticides. The present study highlights the methodology developed for the first time in India for assessing the acute inhalation toxicity of pressurized aerosol insecticide formulation, containing malathion A.I. 1%, Pyrethrin 0.05% and propellant gas solvent and perfume QS, by using the Rhema labortechnik Inhalation Equipment (head exposure) for rat. An electrical device with an electronic timer was designed and used to actuate the pressurized aerosol can for the generation of test atmosphere. Rats were exposed for 4 hr continuously. The concentrations of the test material were 1.208, 1.665 and 2.38 mg/l air at the level of breathing zone of rats. Experimental results showed that rats were able to tolerate 2.38 mg/l concentration of test material without exhibiting any adverse effect.

It was concluded that the methodology developed could be exploited for risk assessment of pressurized aerosol formulations of pesticides, drugs, cosmetics, detergents, etc.

CATEGORY B
METHODOLOGICAL ISSUES IN DESIGNING AND CONDUCTING STUDIES WITH LABORATORY ANIMALS
POSTERS

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Datum, Unterschrift 9.Apr.87 Rq

DUAL WAY CHARACTERIZATION OF AEROSOLS BY THE GALAI-CIS-1 - A POWERFUL TOOL FOR INHALATION EXPOSURES.

E.F.Aharonson, O. Bernstein and N. Karasikov, Israel Institute for Biological Research P.O.Box 19, Ness-Ziona 70450 and Galai Labs Inc. Migdal Ha-Emek, ISRAEL.

Atmospheres of controlled steady and well defined suspensions of hazardous materials in air, to which groups of animals can be exposed, form the basis for studies of inhaled toxicity of aerosols. Characteristics of the aerosol challange are then correlated with the harmful biological responses observed in the exposed animals.

Characterization of aerosols at the point of generation and at the point of delivery is therefore essential for the interpretation of inhaled toxicity experiments. Two parameters are of primary interest: the aerosol concentration and its particle size distribution. In addition, particle's shape may have to be considered. These parameters, size, shape and concentration can be optimally estimated and continuously monitored by the Galai-CIS-1 (Galai, Israel).

The CIS-1 analyser uses a minute actual sensing volume, therefore it remains operational when measuring much higher aerosol concentrations than those acceptable by any other commercial instrument. For most inhalation studies, this feature considerably reduces the need for diluting the sampled aerosol. Moreover, this instrument combines two independent measurements, taken at the same flow through cell, to characterize the aerosol particles population: one estimates particle dimensions from the measured transition time required for a fast moving focussed laser beam to pass across particle's diameter. The other derives shape information from a video two-dimensional image of particles, taken by a CCTV camera and strobed illumination. The combined data proves to be very efficient in describing aerosol populations, especially for non-spherical particles.

Operation of this computerized analysing system is practically fully automatic, enabling to complete the measurment according to a predetermined protocol and storing the results without operator's intervention.

A SYSTEM FOR THE EXPOSURE OF MICE TO TOXIC AEROSOLS

A. Black, J.N. Pritchard and M. Walsh

Environmental & Medical Sciences Division, A.E.R.E. Harwell, Oxon, England

An exposure suite for the nose-only exposure of mice to radioactive aerosols has been in use at Harwell for over 8 years. During this time, some 10,000 mice have been exposed with only 30 fatalities and no incidents of contamination to the personnel involved. Details of the exposure chamber, the facility in which exposures take place and a simple technique for producing size-classified samples of material for exposure has been published (Walsh et al., 1980). A poster display summarising this publication is available.

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Datum, Unterschrift 9.Mai.87

EFFECT OF DIURNAL OR NOCTURNAL OZONE EXPOSURE ON THE PULMONARY RESPONSE OF RATS - L.van Bree, P.J.A.Rombout, M.Marra, P.H.B.Fokkens, A.J.F.Boere and J.Bos, National Institute of Public Health and Environmental Hygiene, Department of Inhalation Toxicology, 3720 BA Bilthoven, The Netherlands.

The biological response of toxic compounds is known to depend on the daily time period of administration. Animal toxicology studies on air pollutants frequently involve exposure during the photolight-period (daytime). However, when nocturnal animals are used, a diurnal exposure will parallel a minimal ventilatory activity and thus a minimal pollutant uptake. Circadian rhythms in biochemical activities may also affect the toxic response. Since air monitoring data for ozone reveal diurnal human exposure periods, animal toxicology studies have been initiated to investigate the role of circadian rhythm in ozone toxicity. In the present study rats were exposed to 0.80 mg O_3/m^3 for 12 h diurnal, 12 h nocturnal or 24 h continuous periods. Increases in pulmonary antioxidant enzyme activities and accumulation of proteins and inflammatory cells in bronchoalveolar fluid were taken as toxicity parameters. Diurnal exposure for 3 days caused no change in enzyme activities; the significant increases (15-30%) after nocturnal or continuous exposure were comparable. A single exposure for 12 h resulted in a nocturnal-mediated increase of protein and albumin in lung lavage fluid (500 and 900% respectively), which was twice that after diurnal exposure. A differential cell count of the lavage fluid indicated that the relative influx of inflammatory cells after nocturnal exposure (1400%) was larger than the diurnal response (600%), while the total cell content was only marginally affected.
These data show large susceptibility differences in pulmonary response depending on the daily time period of ozone exposure. The nocturnal-mediated response is dominant over the diurnal response and may thereby largely govern the continuous exposure-induced effect. Results also emphasize that in animal toxicology studies with air pollutants there is a need for suitable exposure regimens, which synchronize with the actual human exposure and activity pattern.

FACTORS AFFECTING PARTICLE CLEARANCE FROM THE RAT LUNG - C G Collier, A Hodgson, M R Bailey and S F Barry, National Radiological Protection Board, Chilton, Didcot, Oxon OX11 0RQ, UK.

Constraints on the design and conduct of inhalation studies using laboratory animals may introduce factors which could affect the results of the experiments. The effects of physical exercise and method of administration on particle clearance were studied for six months after intake in male and female rats. Monodisperse fused aluminosilicate particles (FAP) labelled with cobalt-57 (half-life 272 d) were used as relatively inert test particles. Lung clearance was followed by measuring the amount retained in the lung by external counting of gamma-rays, complemented by measurements of the tissue distribution of cobalt-57 in sacrificed animals, and by measurements of urinary and faecal excretion of cobalt-57. No effect on clearance of voluntary exercise (running in a wheel), and no difference between males and females was observed. Clearance was significantly faster following intratracheal installation of particles than after inhalation for the first 30 days after intake, but not thereafter.

In earlier experiments we found that lung clearance up to 18 months after inhalation of a mixed actinide oxide containing plutonium-239 and americium-241 was very similar to that of FAP when the total alpha activity of the initial lung deposit (ILD) of the oxide was about 0.1 kBq. At an ILD of 2 kBq clearance of the actinide oxide was impaired, and at an ILD of 9 kBq, clearance of the actinide oxide and also of FAP inhaled 25 days after the oxide were impaired.

This work was partially supported by the CEC under contract B16-0089-UK.

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Source: https://www.industrydocuments.ucsf.edu/docs/fmhl0000

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Bestätigung der Übereinstimmung mit dem Original
Datum, Unterschrift 9.Apr.87

OUTLINE OF FACILITIES AND ACTIVITY OF JAPAN BIOASSAY LABORATORY - K. Nozaki, E. Nakayama and M. Enomoto, Japan Bioassay Laboratory, Kanagawa, Japan

Japan Bioassay Laboratory was founded in 1981 with the aim of investigating the effects of new chemicals on workers' health by means of animal experiments. In addition to carrying out toxicity and carcinogenicity tests to meet the requirements of regulatory authorities, Japan Bioassay Laboratory is studying on mutagenicity and genotoxicity of chemicals by using microorganisms and mammarian cells.

Half of the animal experiments in the laboratory is planned to be performed by inhalation and the other half by oral route. Inhalation test areas consist of 14 long-term inhalation test rooms, 4 short-term inhalation test rooms. 100 rats or mice, each of them kept in a cage with partition, are housed in one long-term test chamber of 7.5 m^3 in volume for rat or 3.5 m^3 for mouse. Inhalation test room for long-term toxicity or carcinogenicity has 4 of this kind of chamber, respectively.

All the animal rooms are located on the 1st floor, which is cleaned with barrier system. Mechanical facilities control center and generator of test aerosols with air conditioning are centralized on the 2nd floor. All the gases or particulate toxicants are supplied from 2nd floor to chambers of 1st floor by monitoring their concentrations and environmental parameters of the chambers. All toxicology data including pathological findings are recorded by centralized computer systems.

Currently, 6 chemicals are tested on their carcinogenicities in both rats of F344 strain and mice of BDF1 strain, respectively.

AN EXPERIMENTAL RABBIT MODEL FOR STUDYING ACUTE EFFECT OF ENVIRONMENTAL IRRITANT AEROSOLS AND GASES ON RESPIRATION, HEART AND CIRCULATION.

M. S. Islam, D. Haake, F. J. Reiffer*

So far we have not come across a report on acute effects of environmental irritant aerosols and gases in experimental rabbits. Secondly most of the previous studies were chronic in nature i.e. long exposure time. To our knowledge two groups have used short (60 minutes) exposure of guineapigs (Amdure et al. 1976) and dogs (Islam et al. 1972) to sulfurdioxide (SO2). So we have made an attempt to develop a rabbit model suitable for studying acute effects on airways, respiration and circulation.
We started this study with 15 animals. But we had to sacrifice two animals prematurely as they suffered from leg fracture in animals house, and another two developped acute respiratory distress before they were exposed to SO2-inhalation. So we could complete our protocol in the remainder of 13 animals.
After application of anesthesia and minor surgical manipulation, for inserting arterial, oesophageal catheters and so on, the animals were left undisturbed for 40' to reach steady state.

After that the animals were exposed to 0, 1, 2, 4 and 9 mg/m^3 SO2 for 5 minutes inhalation at each occasion with periods of at least 20 minutes of recovery. Various cardio-respiratory parameters were registered before, and after o,5', 10' and 20' of exposure with a 6 channel recorder.

Clear increase in lung resistance (Rl) and decrease in dynamic lung compliance (Cldyn) were noted following exposure to SO2.

So the results are contradictory to conventional concepts of a concentration effect pattern, that assume linear or otherwise proportional effects toward increasing exposure. Our results represent a preliminary evaluation of data which will be extended being available soon by completing the study protocol for an experimental rabbit model to investigate the effects of environmental irritants.

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Bestätigung der Übereinstimmung mit dem Original
Datum, Unterschrift 3.Mai.87 Rg

INHALATION TOXICITY STUDIES OF FORMALDEHYDE IN RATS: 8-HOUR CONTINUOUS VERSUS 8-HOUR INTERMITTENT EXPOSURES

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Inhalation toxicity studies with formaldehyde were performed to investigate whether excursions of the exposure concentration by a factor 2 - under conditions of concentration x time is constant - visibly affect the cytotoxic action of formaldehyde on the rat nasal epithelium. A subacute (4-week) study, using clearly cytotoxic concentrations (5, 10 or 20 ppm), and a 13-week study with (sub)cytotoxic concentrations of formaldehyde (1, 2 or 4 ppm) were carried with male Wistar rats. The animals were exposed either continuously for 8 hours a day or interruptedly during 8 successive 1-hour periods (each period consisting of 30 min of exposure and 30 min of non-exposure), 5 days/week during 4 or 13 weeks, respectively. Cell turnover rate (^{3}H-thymidine labeling) in nasal epithelial cells was determined after 3 exposure days and at the end of the 4-week or 13-week experimental period. Histopathology of the nose was carried out at the end of the experimental periods. Treatment-related changes in the nose comprised disarrangement and squamous metaplasia of the respiratory epithelium, accompanied by basal cell hyperplasia. Two ppm formaldehyde was a no-toxic effect level in the 13-week study. From the results of both the 4-week and the 13-week inhalation studies it was concluded that the exposure concentration rather than the total dose is primarily responsible for the adverse effects of formaldehyde on the nasal epithelium.

ANIMAL INHALATION FACILITIES AND EXPERIMENTAL DESIGN FOR DIESEL ENGINE EMISSIONS

T.SUZUKI, T.NAKAJIMA, Y.SUEYOSHI, S.ISHIWATA, (HERP), Japan Automobile Research Institute, Yatabe, Tsukuba-gun, Ibaraki, Japan.

Long-term inhalation studies on the effects of diesel emissions on F344 rats were carried out from January 1983 to December 1985. For these studies, we constructed inhalation facilities which consisted of supply, exposure, exhaust, control and monitor systems.

The light-duty (LD) engines were 1.8-liter, 4-cylinder, swirl chamber type and were operated at 1,700rpm, 4kg·m. The heavy-duty (HD) engines were 11-liter, 6-cylinder, direct injection type and were operated at 1,200rpm, 35.4kg·m. Five LD engines and two HD engines were used during the inhalation experiments. The diesel fuel was JIS No.1 or No.2 light oil with a sulfur content of 0.43%.

Diesel emissions were directed into each dilution tunnel where they were diluted about 10 to 15 times in volume with conditioned air.

Ten large (horizontal type, 3.1m^3) and five middle (vertical type, 2.8m^3) size inhalation chambers were installed in the barrier. One large chamber which was developed for these experiments contained two inhalation spaces, so it could house 120 males on one side and 120 females on the other side. Five middle chambers each housing 64 rats were used for carrying out particle influence experiments.

The diluted emissions in each camber were controlled concering the particle concentrations. From the HD engines, five levels of diluted emissions, 4, 2, 1, 0.4 and Omg/m^3 (Omg/m^3 was the chamber control) were used. Similarly, five levels, 2, 1, 0.4, 0.1 and Omg/m^3 were used from the LD engine.

The gases and particle concentrations for each experimental group were monitored every two hours. The mass median diameter of the particles in the large chambers was in the range of 0.19μm-0.34μm and more than 80% of the particles had diameters smaller than 1μm. The average quantities of benzo-(a)pyrene in the extracts of the diluted emissions were 4.4μg/g and 2.8μg/g, and the average quantities of 1-nitro-pyrene were 57.1μg/g and 15.3μg/g in the LD and HD series, respectively.

Experimental animals inhaled diluted emissions for 16 hours /day, 6 days/week. The total number of animals was about 3,800, inclusive of the breeding room control.

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Datum, Unterschrift 9.Apr.87 Rg

DESIGN AND PERFORMANCE CHARACTERISTICS OF AN INHALATION CHAMBER FOR THE EXPOSURE OF SMALL LABORATORY ANIMALS TO LOW CONCENTRATIONS OF AIR POLLUTANTS - M. Marra, P.J.A. Rombout and H.W. Balfoort, National Institute of Public Health and Environmental Hygiene, Department of Inhalation Toxicology, 3720 BA Bilthoven, The Netherlands.

A 0.2 m^3 inhalation chamber was designed for whole body exposure of laboratory animals, housed permanently. The chamber was constructed of stainless steel and glass and was equiped with inlet and outlet manifolds to obtain even distribution of the incoming air.
A mathematical model was used to determine the flow and mixing characteristics. The exhaust concentration as the respons to a negative step change in inlet concentration was recorded. From the plot of concentration versus time it was calculated that the chamber has an active mixing volume of 80 %, a dead volume of 5 %, and plug flow in 15 % of the volume. Short circuiting between inlet and outlet was not detected.
The distribution within the chamber was determined by measuring the actual concentrations at 12 locations close to the animals. The tests were performed with the oxidants nitrogendioxide and ozone and with a 0.8 um latex aefosol. The spatial variation of nitrogendioxide concentrations was 4 % at 200 $\mu g/m^3$ and even better at higher concentrations. The variation in ozone concentration was 10 % at 150 $\mu g/m^3$ and decreased to 5 % at 400 $\mu g/m^3$. Latex concentration (140 particles/cm^3) varied about 8 %. Additional tests will be carried out with larger particles to determine whether this chamber can be used for inhalation toxicology research with aerosols.
The time in which the concentration in the exposure chamber reached 95 % of the desired concentration was 4.8 minutes. For all measurements the flow rate through the chamber was adjusted to 6 m^3/h, and 10 to 20 rats of approximately 200 g were housed in the chamber.
The design and characteristics of the exposure chamber and its performance were found to make it suitable to expose small laboratory animals to ambient concentrations of oxidant gases according realistic profiles.

A NEW INHALATION APPARATUS DESIGNED FOR DOSE RATE RESPONSE APPLICATION TO TOXICITY STUDY OF VOLCANIC ASH - R.Nagata and M.Niizeki . Shin Nippon Biomedical Laboratories Ltd., Kagoshima 891-1 and * Shibata Scientific Technology Ltd., Tokyo 110, Japan.

We have recently designed an unique nasal exposure chamber capable of utilizing in toxicological studies and the evaluations . The present study was attempted to investigate the acute toxicity of Mt.Sakurajima volcanic ash in beagles. The volcanic ash was inhalated at a dose of approximately 100mg/m^3 as the highest dose in nature. The volcanic ash filtered until become less than 20 μm for aerosol sizes was exposed for six hours. Classification of aerosol sizes and concentration of air bone particle were measured by Andersen type cascade impactors and by digital dust indicator which indicates the relative concentration. Following the inhalation, the animals were examined on general conditions and clinical signs, hematological and blood biochemical examinations, histopathology light and electron microscopy . The histopathological results revealed that a slight inflammatory change in the respiratory system which seemed to be the major toxicity at a high dose inhalation, and also some clinical signs were observed, however they were not supposed to be idiopathic changes even though the volcanic ash would reach as a foreign substance to the respiratory tract. Taken together, the present results suggest that Mt. Sakurajima volcanic ash has low acute toxicity.

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Datum, Unterschrift 9.4.87

THE EFFECT OF RESTRAINT IN NOSE-ONLY EXPOSURE TUBES DURING PREGNANCY ON TERATOGENIC ENDPOINTS IN SPRAGUE DAWLEY RATS - A.I.Nikiforov and G.Allgöwer, Battelle, Centre for Toxicology & Biosciences, route de Drize 7, 1227 Carouge/ Geneva, Switzerland

Evaluations of the teratogenic potentials of chemicals and drugs with inhalation as the route of exposure are becoming more common. In this regard, the method of nose-only inhalation exposure has an advantage over whole-body inhalation exposure in that quantitative dose to the lung can be estimated with the former.

Five exposure groups of 20 pregnant rats each were used in the experiment. The groups consisted of cage air controls, nose-only exposure restraint tube air controls, and nose-only exposure restraint tube groups exposed to different concentrations of carbon disulfide All rats, except the cage controls, were put into the restraint tubes four hours per day on days 6 through 15 of their gestation period. When not in the restraint tubes, these rats were housed under the same conditions as the cage air controls.

The results indicated lower body weights, and significantly fewer viable fetuses in the groups that were restrained, as compared to the cage air controls. Currently the fetuses from all groups are being examined for more subtle effects of soft tissue and skeletal abnormalities.

A second experiment has been initiated to determine whether acclimatization to restraint tubes, before the critical period of organogenesis will allow nose-only inhalation exposure methods to be used without affecting fetal viability or development. These results will also be reported.

NUMERICAL AND GRAVIMETRIC DETERMINATIONS OF ASBESTOS IN AIRBORNE PARTICULATE: A STUDY ON THE COUNT-TO-MASS CONVERSION FACTOR FOR CHRYSOTILE FIBERS - S.Puledda and A. Marconi, Istituto Superiore di Sanità, Rome, Italy.

X-ray diffraction (XRD) by the silver filter method was used to detrmine the gravimetric content of airborne fibers of chrysotile asbestos. The numerical content of the fibers was measured by phase contrast optical microscopy (PCOM) according to the procedure indicated by the Asbestos International Association.
The data obtained by the two procedures permitted to calculate a count-to-mass correlation coefficient. The importance of this factor derives from the following considerations: the numerical method supplies the most specific parameters for the asbestos biological effects, but is scarcely precise and time-consuming. If a satisfactory correlation between the two methods - optical and diffractometric - can be found in a given situation, the use of the latter, which is faster and more precise, can be justified also from a toxicological point of view.
In this work, nine samples of airborne particulate were collected on normal cellulose filters at the outlet of an asbestos-cement industrial plant using only chrysotile asbestos. A fraction of the filter was ashed in a low temperature asher. The residue was dispersed, deposited on a silver filter and XRD-analyzed. Another fraction was adequately prepared and observed by PCOM.
The average value for the correlation coefficient was: 1.9 ± 1.2 ff/ug x 10^3.

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HEALTH EFFECTS OF DIESEL EXHAUST: THE INFLUENCE OF ENZOOTIC INFECTIONS ON THE INCIDENCE OF PRIMARY LUNG TUMORS IN DIESEL EXHAUST EXPOSED MALE RATS - O. R. Moss, B. J. Greenspan, R. H. Busch, R. L. Buschbom, S. E. Rowe, Battelle, Pacific Northwest Laboratories, Richland, WA 99352 and R. M. Schreck, Biomedical Science Department, General Motors Research Laboratories, Warren, MI 48090.

The purpose of the study was to investigate the carcinogenic potential of diesel engine exhaust. Animals were maintained in two ways: in a manner which provided a high level of protection from exposure to rodent pathogens; and under reduced barrier conditions that could allow natural enzootic infections to occur. We were concerned that the nature of the animal care would influence the outcome of the experiment. For each of the two animal care conditions, one group of 288 male F344 rats were exposed to 1500 $\mu g/m^3$ of diesel particles, and another group of the same size was air exposed. The duration of exposure was twenty hours per day, seven days per week, for fifteen months followed by a clean air holding period of eight months. The exhaust was generated from a General Motors 4.3-liter indirect injection engine operating under conditions of steady speed (1475 rpm) and torque (63 N-m).

After one year, the animals maintained under reduced barrier conditions showed strong ELISA positive reactions to Sendai virus antibody. The exposed group of these animals was the only group that showed a statistically significant decrease in mean survival time. There were no significant findings for the serologic tests or for the mean survival times in the other animals. In all of our barrier protected exposed and control groups, the incidence of primary lung tumors was less than 2%. In the reduced-barrier animal groups, the controls had a 2% incidence versus a 3% incidence of primary lung tumors in the exposed animals. The differences in the incidence of primary lung tumors between all test groups were not statistically significant.

HEALTH EFFECTS OF DIESEL EXHAUST: THE INFLUENCE OF AGE DURING EXPOSURE ON THE INCIDENCE OF PRIMARY LUNG TUMORS IN DIESEL EXHAUST EXPOSED MALE RATS - O. R. Moss, B. J. Greenspan, R. H. Busch, R. L. Buschbom, S. E. Rowe, Battelle, Pacific Northwest Laboratories, Richland, WA 99352 and R. M. Schreck, Biomedical Science Department, General Motors Research Laboratories, Warren, MI 48090.

The purpose of the study was to investigate the carcinogenic potential of diesel engine exhaust. Animals were maintained in a manner which provided a high level of protection from exposure to rodent pathogens. Animals received diesel exhaust exposures during the first fifteen or the last fifteen months of their lives followed by immediate sacrifice. We were concerned that the age of the animals during exposure would influence the outcome of the experiment. Each of the three exposed groups consisted of 288 male F344 rats. These animals were exposed to 1500 $\mu g/m^3$ of diesel particles. One additional group of the same size was air exposed. The duration of exposure was twenty hours per day, seven days per week, for fifteen months. The aged exposure group received clean air until the two young exposure groups had been exposed for eight months. This group then began a fifteen month exposure period. One of the young exposure groups was sacrificed immediately and the other received clean air for eight months following exposures. The exhaust was generated from a General Motors 4.3-liter indirect injection engine operating under conditions of steady speed (1475 rpm) and torque (63 N-m).

There were no significant findings for the serologic tests or for the mean survival times in the animals. In all of our exposed groups, the incidence of primary lung tumors was less than 3%. There was no significant difference in the incidence of primary lung tumors in the control and aged-exposed group or in the young exposed group held for eight months and sacrificed at the same time.

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Bestätigung der Übereinstimmung mit dem Original
TNO Datum, Unterschrift 9. Apr. 87

EXHALATION RATES OF VOLATILE N-NITROSAMINES IN COMPARISON WITH NITROSAMINE BLOOD LEVELS AFTER DIFFERENT MODES OF APPLICATION IN RATS - R.G.Klein, B.Schmezer, P.Schmezer, B.Spiegelhalder, and D.Schmähl, Institute of Texicology and Chemotherapy, German Cancer Research Center, 6900 Heidelberg, Im Neuenheimer Feld 280.

Volatile N-nitrosamines may be a possible risk factor in human carcinogenesis after occupational exposure at certain working places. The major route of absorption into the organism is expected to occur via inhalation. Therefore we investigated several nitroso compounds relevant for the human situation by endotracheal intubation to rats. With this mode of application inhaled substances proceed directly into the trachea and the lungs of the animals, without being absorbed in the nasal region and the larynx. Furthermore exhaled air can be collected directly from the respiratory tract. We compared the distribution of N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitrosopyrrolidine (NPYR) and N-nitrosomorpholine (NMOR) in blood and in exhaled air after applying comparable dosages of the compounds by endotracheal inhalation and by intravenous injection., Following endotracheal inhalation remarkable amounts of the applied nitrosamines were found in the exhaled air: NDMA: inhal. 600 ug, exhal. 6ug (1%), NDEA: inhal. 550 ug, exhal. 2ug (0.4%), NPYR: inhal. 850 ug, exhal.40ug (5%) and NMOR: inhal. 520 ug, exhal.20 ug (4%). Extraploation of these values to the first breath just after inhalation led to results indicating that more than 10% of the applied dosage can be exhaled. After intravenous injection of the same amount of nitrosamine into the tail vein of the animals the exhaled amounts were much smaller: e.g. NMOR: iv 520 ug, exhal. 40 ng (0.008%). After iv injection of 520 ug of NMOR blood values of 0.8 ug (0.2) were found. In comparison: after endotracheal inhalation of 520 ug of NMOR 0.1 ug (0.02%) was found in blood. All values were gained by pooling the results from 5 animals. Because of the well defined water solubility of the nitrosamines (NDMA, NPYR and NMOR 100%, NDEA, 10%) we must conclude that solubility properties are not the only factor decisive in the absorption of the compound by the animals' respiratory tract. This is supported by the finding that the thermodynamic defined volatility of the substances is not simply related to the measured exhalation rates. Our results may show an improved way for estimating the actually absorbed amount of nitrosamine during longterm carcinogenicity experiments.

CATEGORY C
INTERPRETATION OF TOXICOKINETIC STUDIES
WITH AIRBORNE TOXICANTS
PAPERS

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2484
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Datum, Unterschrift 9.4.87

NTERSPECIES DOSIMETRY OF REACTIVE GASES - F.J. Miller, J.H. Overton and T.R. Gerrity, U.S. EPA, Research Triangle Park, NC 27711 and R.C. Graham, NSI-ES, Research Triangle Park, NC 27709

The development of dosimetry models that can provide a description of the uptake and distribution of inhaled compounds throughout the body and the availability of animal toxicological data are integral components for a full evaluation of potential risks associated with human exposures. Interspecies dosimetric comparisons must be approached using a model conceptualization that incorporates the major factors affecting the uptake of the gas, such as respiratory tract morphology, route of breathing, depth and rate of breathing, physicochemical properties of the gas, etc. When studying the lower respiratory tract uptake of highly reactive gases, additional complexities are introduced in treating mass transport since variations in thickness and biological composition of the airway lining can yield a significantly altered dose to the underlying tissue compared to the net mass removed in an airway. Modeling efforts thus far have primarily focused on ozone. Hence, this gas will be used to illustrate the methodologies needed to develop dosimetry models for other reactive gases and to discuss various aspects of delivered dose. A comparison of theoretical predictions of delivered dose of ozone to the lower respiratory tract of man shows good agreement with dose estimates derived from experimental measurements. Applications to ozone toxicological data in animals and man have been examined that incorporate the use of dosimetry models in studying quantitative dose-response relationships. Published data on exercise-related decrements in forced expiratory volume (1 sec) of healthy adult subjects were related to the total tissue dose for ozone exposure levels ranging from 0.12 to 0.4 ppm. Accumulation of protein in lavage fluid obtained from guinea pigs, rats, and rabbits exposed to various concentrations of ozone were related to predicted pulmonary tissue dose/g body weight to enable an assessment of the relative sensitivity of these species to ozone. The results indicate that rabbits and rats respond similarly for this biological endpoint with guinea pigs being more responsive. This is an abstract of a proposed presentation and does not necessarily reflect EPA policy.

DEPOSITION OF INHALED PARTICLES IN MAN - J.Heyder, GSF-Projekt Inhalation, Paul-Ehrlich-Str.20, D 6000 Frankfurt am Main 70

The human lung can be considered as an effective aerosol filter. Its characteristics (efficiency, ventilation pattern, dimensions) may be altered by the inspiration of toxic materials. However, this knowlege has not sufficiently been used to develope methods for assessing inhalation risks.

This paper is focussed on the current understanding of particle behaviour and collection in the human respiratory tract and on aerosol techniques which allow, in subjects with healthy and affected lungs, to study particle collection efficiencies and ventilation patterns of the lungs and to estimate thoracic airway dimensions.

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TOXICOKINETICS OF NON-REACTIVE GASES - M. E. Andersen, Toxic Hazards Division (AAMRL/TH), Wright-Patterson AFB, OH 45433.

The lung is a target organ and a route of entry for airborne chemicals. Non-reactive vapors are absorbed by respiration and transported to systemic tissues via the blood. Tissue exposure to these inhaled chemicals is complexly related to physiological, biochemical, and physical chemical factors. Physiologically-based pharmacokinetic (PB-PK) models have been used to gain insights into how these various factors regulate the kinetics, metabolism, and toxicity of inhaled, non-reactive vapors. PB-PK models contain more biological detail than traditional data-based compartmental PK models and allow more complete analytical description of the disposition of inhaled vapors in vivo. This talk focuses on PB-PK modeling studies of the inhalation of three chemicals - styrene, hexane, and methylene chloride. With styrene, metabolic saturation and high lipophilicity produce striking concentration-dependent kinetic behavior. With hexane (Hx), there are complex, time dependent inhibitory interactions which occur because both hexane and its metabolite methyl-n-butyl ketone are competitive substrates for microsomal oxidation. The methylene chloride model contained two pathways for tissue metabolism - oxidation and glutathione conjugation - and also included production of carbon monoxide (CO) and CO binding to hemoglobin. The complex kinetic behaviors of all three chemicals and the major metabolites of Hx and CH_2Cl_2 were easily incorporated into PB-PK models which then provided a more thorough understanding of the dominant biological processes involved in the disposition of these particular chemicals. PB-PK models based on knowledge of animal physiology, tissue solubilities, and limited in vivo experiments predict kinetic behavior. Even when a predictive model fails to agree with data, the nature of the deviation can be very informative of biological processes, as will be illustrated by our studies of suicide enzyme inhibition during exposure to cis- and trans-1,2-dichloroethylene. In summary, PB-PK modeling integrates a variety of data on a test vapor to produce a predictive description of chemical behavior that can be used for extrapolation, experimental design, and interpretation of toxicity results.

RESPIRATORY TRACT CLEARANCE OF PARTICLES AND SUBSTANCES DISSOCIATED FROM PARTICLES - R.G. Cuddihy, Lovelace Inhalation Toxicology Research Institute, Albuquerque, NM 87185.

To discuss the deposition and clearance of inhaled aerosols, the respiratory tract is generally subdivided into the head airways, tracheobronchial airways and pulmonary region. Within each subdivision, clearance is the net result of competing mechanical transport and absorption processes. The nasal airways clear within hours and a large portion, 60% to 80% of the deposited material, moves forward toward the nostrils. The remainder is cleared toward the oropharynx and is swallowed or it is absorbed directly into blood. Deposition and clearance of material in tracheobronchial airways is determined by similar mechanisms and can be predicted using principles of aerosol physics, airway morphometry and effective particle clearance velocities for individual airways. A few percent of the deposited material may be retained for long periods of time in the epithelium of the head and tracheobronchial airways, but this may result from damage to the epithelium or mucociliary clearance apparatus. The rates and fractions of deposited particles cleared by mechanical processes in the pulmonary region are very species dependent, but absorption of material into the blood circulation appears to be similar among species that have been studied. Absorption mainly occurs with material that dissociates from particles; however, some particles may be transported to blood and some dissociated material may be retained in the pulmonary region bound to structural components for long periods of time. A mathematical model describing these clearance processes for people and laboratory animals will be discussed. A computer program is being developed to perform inhaled aerosol deposition and clearance calculations for people, dogs, rats, hamsters and mice, and to modify the calculations to account for different body sizes, health status and cigarette smoking. (Research supported by the Office of Health and Environmental Research, U.S. Department of Energy under Contract No. DE-AC04-76EV01013.)

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Datum, Unterschrift 9. Apr. 87

TOXICOKINETICS OF THE ETHYL ETHERS OF ETHYLENE GLYCOL AND ETHYLENE GLYCOL ACETATE IN MAN. - D. Groeseneken, H. Veulemans, R. Masschelein, Department of Occupational Medicine, Cath. University of Louvain, B-3000 Louvain, Belgium.

The metabolism of ethylene glycol ethers has been studied in several animal models. Human studies, however, are lacking. Therefore, we exposed healthy male volunteers to resp. 10, 20, and 40 mg/m³ ethylene glycol ethyl ether (EGEE) or equivalent concentrations of its acetate ester (EGEE-Ac) for 4h at rest. EGEE or EGEE-Ac was determined in exhaled air during and up to 4h after exposure. Urine was collected over a period of 48h during and after exposure and analyzed for the presence of ethoxyacetic acid (EAA), the main urinary metabolite of both EGEE and EGEE-Ac.
Retention (R) of EGEE was high (64 %) reaching steady-state levels within 10 min. In the case of EGEE-Ac, R was somewhat lower and decreased slowly ($p < 0.01$) as exposure proceeded. Steady-state seemed to be reached after 3-4 h. R of EGEE was not affected by exposure concentration, but R of EGEE-Ac increased ($p < 0.05$) when exposure concentrations were higher. In both cases, uptake rate increased ($p < 0.001$) almost linearly with increasing concentrations, although significant contributions of indices of cardiac output and, in the case of EGEE-Ac also of volume of distribution, were observed. During exposure to EGEE-Ac, small amounts of EGEE appeared in expired air with a half-life of 8-11 min proportionally to the uptake of EGEE-Ac. Post-exposure breath concentrations of both EGEE and EGEE-Ac showed a dramatic drop during the first minutes. Thereafter, a much slower bi-exponential decrease was observed to almost undetectable levels after 4h. Post-exposure breath concentrations of EGEE or EGEE-Ac were higher ($p < 0.05$) as their uptake was higher. Respiratory elimination of unmetabolized EGEE or EGEE-Ac accounted, however, for ≤ 0.5 % of total body uptake. EAA appeared in urine with a half-life of 2-2.5h reaching maximal excretion rate 4h after the end of the exposure in both cases. The decline afterwards could generally be described assuming a half-life of 22-25h. On average 23 % of absorbed EGEE or EGEE-Ac was recovered within 48h. Recovery of EAA did not change on higher uptake. For equivalent doses of EGEE and EGEE-Ac, the same amount of EAA was excreted in urine.
As in animals, EGEE and EGEE-Ac are rapidely absorbed through the lungs and metabolized to EAA. Respiratory elimination of unchanged EGEE or EGEE-Ac was negligable compared to urinary excretion of EAA. Due to the long half-life of EAA, accumulation is expected through repetitive exposures.

INTERPRETATION OF REGIONAL DEPOSITION DATA BASED ON HUMAN - LUNG CLEARANCE STUDIES WITH RADIO-AEROSOL PULSES

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Institut für Biophysikalische Strahlenforschung,
6000 Frankfurt am Main, Paul-Ehrlich-Str. 20

With a new inhalation technique described in a previous paper (Stahlhofen et al. 1986) it is possible to inject 50 cm^3 aerosol boli with defined volumes at any moment during inhalation into the inspired air. By varying the point of injection during inspiration and by holding the breath at end-inhalation deposition of particles in different volumetric lung depths is achieved.

With this pulse technique experiments were carried out with four subjects using different particle sizes. Particle clearance was measured as function of their site of deposition in the lungs.

A surprising result was that there exists a great fraction of deposited particles which are not cleared rapidly even after their injection into the upper airways only. Thus from aerosol boli injected into a volumetric lung depth of about 70 cm^3 only about 60% of the deposited material was cleared in the following 5 days.

Possible explanations for this phenomenon are for instance a particle size dependent mucociliary clearance and ventilation patterns in the upper respiratory tratc (Stahlhofen et al. 1986).

This new experimental data give rise for a critical review of regional deposition data based on measurements of lung clearance.

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Datum, Unterschrift 2.Apr.87

THE EFFECTS OF EXPOSURE MODE ON DUST RETENTION AND ELIMINATION

J.Bruch,E.Gono,Ch.Li,M.Roos, Institut für Hygiene und Arbeitsmedizin Universitätsklinikum der Gesamthochschule Essen, Hufelandstr. 55, D-4300 Essen 1.

The effects of occupational dust exposure vary according to the dust concentration, and wether the exposure is continuous or intermittant. It is suspected that peak concentration of dust might worsen the elimination rate from the lung. The peak exposure, the time integral in combination with the superelevation of the concentration of the dust is to be determined by means of toxicological investigation. The effects of various exposure-time-combinations with nuissance dust and quartz dust exposure were studied in acute and subchronic inhalation experiments. The results provide definition of peak concentration which is related to an excessive increase of pathogenic dust retention and related pathogenic effects.

A MACROPHAGE ASSAY FOR INTRACELLULAR DISSOLUTION OF UNIFORM AEROSOL PARTICLES

W.G. Kreyling, Gesellschaft für Strahlen- und Umweltforschung mbH München, Institut für Strahlenschutz, D-8042 Neuherberg, FRG; J.J. Godleski, S.T. Kariya, J.D. Brain, Harvard School of Public Health, Respiratory Biology Program, Boston Ma 02115, USA; R.M. Rose, New England Deaconess Hospital, Division of Pulmonary and Critical Care Medicine, Boston, Ma 02115, USA.

The dissolution of inhaled particles in the lungs with subsequent translocation of this material to the blood is considered to be an important clearance pathway (ICRP 30). For relatively insoluble particles, the dissolution process is slow and is carried out primarily by intracellular digestion in phagolysosomes of macrophages. In these studies we determined the dissolution rate of uniform, porous, Co-57 labelled, cobaltosic oxide particles in cultured alveolar macrophages.
Canine and human macrophages were harvested by bronchoalveolar lavage and cultured in RPMI 1640 media with 5% fetal bovine serum. Particles with a geometric mean diameter of 0.3, 0.7, 0.8, or 1.7 um were added to the cell monolayer such that all particles were phagocytized within 2 days. Samples were taken at 5 time points between day 4 and 14, and the dissolved cobalt fraction was determined by means of filtration and tracer activity measurements. The extracellularly released, dissolved fraction increased with time, whereas the intracellular fraction remained constant resulting in a transition half-time of 0.5 day for dissolved Co in the cells. At each time point, functional parameters were tested to assure that the cultured cells were alive and healthy. Since integral dissolved fractions increased with time, we calculated a dissolution rate. For each particle size this rate was characteristic and varied from 0.2 to 8 % per day for the largest and the smallest particles, respectively. This was found to be valid for alveolar macrophage samples from 6 different dogs and 2 human volunteers.
These in vitro dissolution rates were very similar to in vivo dissolution rates determined in previous clearance studies after inhalation of corresponding aerosols. Therefore, an important clearance mechanism, the intracellular dissolution of inert, relatively insoluble particles in the lungs, can be assayed using pulmonary macrophages in vitro.
(Supported by NIH Grant ES-00002.)

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Bestätigung der Übereinstimmung mit dem Original
Datum/Unterschrift 8 Mai 87

IN VITRO SOLUBILITY OF PARTICLES USING CULTURED ALVEOLAR MACROPHAGES. COMPARISON WITH IN VITRO A CELLULAR MODEL AND DATA OF IN VIVO SOLUBILITY. - S. André, H. Métivier, G. Lantenois and R. Masse, CEA/IPSN/DPS/SPE/Section de Toxicologie et Cancérologie Expérimentale, BP 12, Bruyères le Châtel, 91680, France.

Knowledge of the lung solubility of metallic particles is of considerable interest to predict their translocation rate from lung to blood and the toxicokinetic of the material inhaled. Unlike the in vitro model of solubility which attempted to simulate the alveolar environment with chemicals, we investigated the capacity of rat alveolar macrophages to dissolve metallic particles. Comparison was made between the dissolution rates obtained with such cellular in vitro experiment, those obtained with in vitro model using chemicals and finally those obtained from metabolic experiments. The capacity of alveolar macrophages to dissolve two different samples of heterodisperse beryllium particles (beryllium metal after refining and hot-pressed beryllium metal after machining) was studied with bronchoalveolar lavaged cells (BAL cells) of rats from the Wistar AG strain. After removal from the lung, BAL cells were allowed to adhere on the bottom of the culture flask in RPMI medium supplemented with 10-15% of foetal calf serum. Beryllium particles were added to the culture 24 hours later according to the ratio : particles/adherent cells 2:1 and phagocytosis was observed within the two hours following their addition. During a 10 day period, the supernatants of the cell cultures and controls were removed daily, filtered through a 0.45 µm filter, and beryllium concentration was analyzed by Flameless Atomic Absorption Spectrometry. The results of our dissolution test with cultured macrophages demonstrate that they were intensively involved in beryllium particles dissolution, since 10.10^6 cells dissolve 10 to 20 times more beryllium than the same medium without macrophages. The results of the in vitro experiments with a serum simulant did not correspond with those observed in vivo which clearly showed that solubility of hot-pressed beryllium is 4 times higher than those of beryllium metal. On the other hand macrophage dissolution was a better method than the in vitro tests which did not involve a cellular component since it showed the same trends in the dissolution rates as those observed in vivo.

A NEW MONTE CARLO DEPOSITION MODEL FOR EXTRAPOLATION OF ANIMAL EXPOSURE DATA TO MAN - W. Hofmann and L. Koblinger, University of Salzburg, Austria, and Central Research Institute for Physics, Budapest, Hungary.

The establishment of regulatory standards for airborne toxicants requires accurate estimation of particulate deposition in the respiratory tract. The laboratory rat is often used as a human surrogate to estimate hazard to human health following inhalation exposure to ambient aerosols. Here, we present a new stochastic morphological model for the rat respiratory tract (analogous to that done for the human; Koblinger and Hofmann, Phys. Med. Biol. 30: 541-556, 1985), and conduct random pathway calculations of particulate deposition in the rat and in man. Morphometric data for the rat lung have been taken from measurements done at the Lovelace ITRI. A Monte Carlo method is used to construct an airway geometry along each particle's path by selecting airway parameters randomly from their frequency distributions and the correlations among them. Interspecies similarities and differences in regional depositon patterns are examined as functions of respiratory breathing parameters (i.e. rate and tidal volume).

The potential adverse health effects of inhaled radon progeny is a matter of current global concern. In an earlier work (Hofmann and Martonen, Inh. Part. VI, in press), the significance of localized particulate deposits at airway bifurcations was introduced for radionuclides. Hazard evaluation of radioactive aerosols requires an additional consideration over non-radionuclides; namely, energy distribution within lung tissue. The combined effect of enhanced radionuclide deposition, together with impaired mucocibiary clearance at branching sites (particularly at carinal ridges), suggests that lung cancer risk by inhaled radon progeny is higher at such locations than along tubular airway segments. Our calculations indicate that radiation doses at bronchial bifurcations might be up to an order of magnitude greater than along adjacent airway surfaces. This factor is consistent with experimental results of Cohen et al. (Inh. Part. VI, in press) for Po-210 attached to submicron smoke particles. Here, interspecies dosimetry computations are compared for the rat and man, thereby permitting accurate extrapolation of current animal data to man, and sponsoring the design of future exposure tests.

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CATEGORY C
INTERPRETATION OF TOXICOKINETIC STUDIES WITH AIRBORNE TOXICANTS
POSTERS

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Datum, Unterschrift 9.Mai.87 Rq

THE EFFECT OF A "NUISANCE" DUST INHALATION ON LUNG CLEARANCE

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For particles which show low solubility and/or slight biological effects a general threshold limit is applied in the occupational field, e.g. 6 mg/m3 (FRG) and 5 mg/m3 (USA). These dusts are sometimes also called "nuisance" or "inert" dusts. In this study the effect on lung retention and lung clearance of three typical "inert" dusts, titanium dioxide (rutil), PVC powder and iron powder was determined. The mass median aerodynamic diameters of these particles were 1.2, 1.3 and 5 µm respectively. Female Fischer rats (F344) were exposed nose-only 5 hours/day, 5 days/week at aerosol concentrations of 3.2, 8 and 20 mg/m3 up to 8 months. 1, 3 and 6 months after beginning of exposure 8 animals of each group inhaled additionally a test aerosol of Fe-59 labelled iron oxide particles and in some cases also Sr-85 labelled polystyrene particles. For lung clearance measurement the decrease of x-activity in the thoracic area of these animals was monitored for 85 days. Chronic exposure was continued during this time. Recovery of the lung clearance was investigated two months after ending of exposure. Lung retention of inhaled particles was determined at various times during and after ending of exposure.

The lung burden after 8 months of exposure has been about 7 mg for PVC, 4 mg for titanium dioxide and 0.6 mg for iron powder at the highest concentration. The PVC dust inhalation caused a severe retardation of the long-term lung clearance of labelled polystyrene particles at the medium and high concentration. For iron powder and titanium dioxide inhalation only in the high concentration group a small retardation of lung clearance was detected.

PULMONARY DISTRIBUTION OF DIFFERENT AEROSOL PARTICLES AS A FUNCTION OF TIME AFTER INHALATION BY RATS -

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In order to assess the risk after incorporation of aerosol particles it is essential to know the concentration of the toxicant in the different parts of the lung and its translocation and excretion as exactly as possible. In the present study young female Sprague-Dawley rats inhaled nose-only for two or four hours either spherical Co-oxide particles of two different sizes or U/Pu mixed oxide particles of different shapes (spherical or irregular) and sizes at various dose levels, and were sacrificed between three days and six months after exposure. For Co-oxide the degree of inhomogeneity was higher for the larger particles (AMAD = 2.7 µm) than for the smaller ones (1.4 µm). In case of the U/Pu mixed oxides (0.9 and 1.5 µm) the administered dose (0.4 - 13.1 kBq/kg) had a marked influence on the relative intrapulmonary concentration (% of total lung burden per lobe / % of total lung weight of the lobe). In all the experiments the right apical lobe had the highest relative concentration with a tendency to increase further at later time intervals. The results will be compared in detail with those from other studies [Morgan et al., Rad. Res. 93 (1983) O. Raabe et al., Aerosols: Formation and Reactivity, 2nd Int. Aerosol Conf. Berlin, Pergamon (1986)] on different species, with the aim of broadening the basis for extrapolating from animal studies to an estimate of the potential toxicity of inhaled aerosols in people.

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PHARMACOKINETICS OF INHALED 2-NITROPROPANE IN THE RAT - B. Denk, E. Deml, D. Oesterle, K.H. Summer and J.G. Filser, Institut für Toxikologie, GSF, D-8042 Neuherberg, FRG

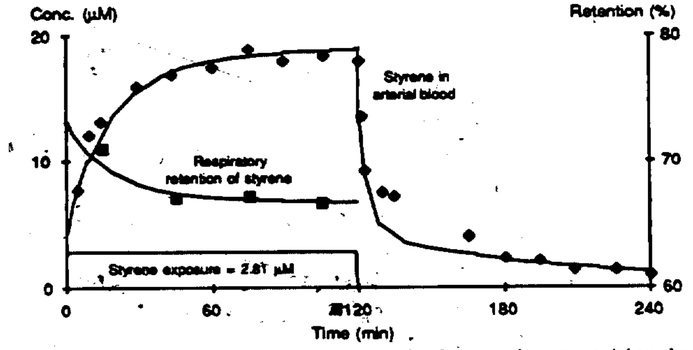
The solvent 2-nitropropane (2-NP) is referred to dose-dependently produce liver necrosis and hepatocarcinoma in the rat. Since this may be caused by reactive metabolites we studied the rate of metabolism in dependency of the atmospheric concentration of 2-NP.
Two male or two female Sprague-Dawley rats were exposed simultaneously to gaseous 2-NP in closed all glass exposure systems (21 l). Due to extensive reaction of 2-NP with the carbon dioxide absorbent soda lime the latter was omitted. The initial gas concentrations ranged from 50 ppm up to 1600 ppm. The concentrations were measured gaschromatographically. Concentration-time-curves were followed over the exposure time up to 3 h. In two experiments the experimental procedure was modified to allow 8 h exposure. Pharmacokinetic parameters were determined as previously described [Simon et al. (1985), Arch. Toxicol. 57, 191].
At all concentrations no saturation kinetics were observed. In both sexes the decay of 2-NP followed strictly first order kinetics. The metabolic clearance correlated with the atmospheric concentration and amounted to 24000 ± 3000 (ml/h·kg b.w., ± S.D.). This value approaches the ventilation rate in this species. The rate of metabolism was directly proportional to the exposure concentration and reached 980 umol/h·kg b.w. at 1000 ppm. From the linear kinetics and the high metabolic clearance it can be deduced that the rate of 2-NP metabolism is mainly limited by pulmonary uptake.
Additionally, at exposure concentrations of up to 100 ppm pretreatment with dithiocarb (200 mg/kg b.w., i.p.), an effective inhibitor of cytochrome P450 mediated metabolism, resulted in an inhibition of 2-NP metabolism by only 60%. This supports in vitro findings that 2-NP metabolism not exclusively proceeds via mixed function oxidases.

PHYSIOLOGICALLY BASED MODELING OF ORGANIC SOLVENT TOXICOKINETICS BY SPREAD-SHEET PROGRAMMING ON A PC - G. Johanson and P.H. Näslund, National Board of Occupational Safety and Health, S-171 84 Solna, SWEDEN.

The principles and advantages of physiologically based kinetic modeling of xenobiotica as well as of inhaled solvents are well established. Many different models and programs have been used, but most are difficult to operate and/or limited in their application. We have developed a concept, where a simple program is run in the form of a spread-sheet program (Microsoft® Excel) macro instruction on a personal computer (Apple Macintosh™ Plus). The model parameters are entered and stored in tabular form, and any variables may be plotted. All parameters and procedures have default values and simulations can be performed by a beginner after a few instructions. With some knowledge of the Excel spread-sheet program and of physiological modeling by defining a set of mass-balance equations, the model can easily be altered or designed in any fashion, e.g. by introducing Michaelis-Menten kinetics, metabolite(s) kinetics etc.

The outcome of the Excel program was identical to that of a Fortran based program intended for the general solution of differential equations (Dare-p), when the same models were run. In terms of processing time, the Dare-p program was somewhat faster. However, considering the total time spent at the computer, the Excel program was much faster.

The concept is illustrated by program listings and graphical results from the simulation of the toxicokinetics of some organic solvents (see example below), although it is applicable for the modeling of the kinetics of any substance in the body. When using this concept the efforts may be concentrated on the problems related to the toxicokinetics of the substance, rather than on the computer and its programming.



Exposure to styrene during light physical exercise on a bicycle ergometer. Comparizon between simulated curve and experimentally obtained values. It took less than 5 min to obtain the plot, counted from the start of the simulation.

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PULMONARY DEPOSITION, RETENTION, AND CLEARANCE OF A PIGMENTED POLYMER IN RATS

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We have defined the Maximum Functionally Tolerated Dose (MFTD) of a material as the lung burden for which macrophage mediated lung clearance is not significantly impaired. In order to establish its value for the pigmented polymer, a 90-day subchronic inhalation study of a toner fraction was conducted by exposure of groups of F-344 rats for six hours/day, five days/week for 13 weeks. The test material used was a specially prepared and characterized powder sample identical to 9000 type xerographic toner, except that its ACGIH respirable fraction was enriched about 10-fold to 35%. The exposure concentrations used were 0, 1.0, 4.0, 16.0, and 64.0 mg/m^3 total mass.

Clearance results for the test material and a superimposed spike of Fe^{59} iron oxide were essentially unchanged at exposure concentrations of 0, 1 and 4 mg/m^3 when measured at different times during the exposure period. At 16 mg/m^3, some indications of slightly retarded iron oxide clearance were noted after 90 days of exposure. At 64 mg/m^3, no appreciable toner clearance was observed after 60 and 90 days of exposure, and clearance of the iron oxide tracer was significantly retarded after 30, 60 and 90 days.

Based upon the above observations, as well as the increase in lung weight, the maximum functionally tolerated dose of test material (MFTD) in this subchronic study was exceeded at the 64 mg/m^3 exposure level.

KINETICS OF THE ACCUMULATION IN THE LUNG AND ASSOCIATED LYMPH NODES OF INHALED MINERAL DUSTS DURING PROLONGED CHRONIC EXPOSURE

J.H. Vincent, A.D. Jones, A.M. Johnston, C. McMillan.
(Institute of Occupational Medicine, Edinburgh, Scotland, United Kingdom).

Experiments have been carried out using laboratory rats exposed to fibrous and non-fibrous, toxic and non-toxic, and relatively-insoluble mineral dusts under chronic exposure conditions for airborne respirable concentrations from 0.1 to 100 mg/m^3. The aim was to investigate the accumulation of dust in the lung and associated lymph nodes. The results have shown consistently that, after an initial non-linear phase during the earlier part of the exposure history, lung burden becomes a linearly-increasing function of exposure time. Furthermore, lung burden scales directly with respect to the respirable concentration over its full range. The corresponding results for the lung-associated lymph nodes suggest that substantial accumulation of dust in them does not begin until lung burden itself has reached a certain threshold. That threshold is lower for toxic than for non-toxic dust. However, once accumulation has begun, the actual rate of transport is not markedly dependent on toxicity.

The experimental results form the basis of an improved mathematical model for the kinetics of accumulation of lung and lymph node burden. The central feature of the model is the sequestration of particles at locations from which they cannot be cleared (possibly by focal aggregation in macrophages in alveolar spaces, entrapment within epithelial cells and in the alveolar interstitium and/or entrapment within areas of fibrotic pathological change).

This model is now being used to explore the relationship between exposure and dose for humans chronically-exposed to mineral dusts in the occupational environment. It provides results which are markedly different from those obtained using previous models.

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CARBON FIBRES: RESULTS OF A FURTHER SURVEY OF PROCESS WORKERS AND THEIR ENVIRONMENT IN A FACTORY PRODUCING CONTINUOUS FILAMENT - H.D. Jones, Courtaulds plc, P.O. Box 16, Coventry, W. Midlands, U.K.

Carbon fibre production was started in 1972. Process workers engaged in all aspects of production have been kept under medical surveillance since the initial start-up, which included radiographic, spirometric and respiratory questionnaire and examination.

Dust concentrations have been low, mean level being 0.39mgm^{-3} total dust and 0.16mgm^{-3} respirable dust, the mean carbon fibre diameter being 8-10μ, fracturing laterally, but not longitudinally into fibrils.

Follow-up results since inception of the producing have revealed no evidence of ill effect on the lungs.

NON-LINEAR RELATIONSHIP BETWEEN THE DOSE DEPOSITED IN THE RESPIRATORY TRACT AND THE DOSE TO TARGET TISSUES. M.A. Medinsky and R.O. McClellan, Lovelace Inhalation Toxicology Research Institute, Albuquerque, NM 87185

Polycyclic aromatic hydrocarbons such as the respiratory tract carcinogen, benzo(a)pyrene are emitted into the atmosphere as a result of fossil fuel, gasoline and diesel fuel combustion. These compounds may pose a health risk to people if inhaled and retained in the respiratory tract. Studies were conducted in which rats were given doses of ^{14}C-benzo(a)pyrene, ranging from 6400 ng per g lung to 16 ng per g lung. Rats were sacrificed at various times after administration and the total ^{14}C in the lung and ^{14}C covalently bound to macromolecules was determined. Two-component negative exponential functions were fit to the data obtained. With increasing dose (16-6400 ng), an increasing percent (89-99.76) cleared with a short half-time (less than 1 day) and a decreasing percent (11-0.24) cleared with a half-time greater than 1 day. Equilibrium levels of benzo(a)pyrene in lungs, predicted for continuous exposure to benzo(a)pyrene, ranged from 3.3 to 100 ng/lung (a factor of 30), although the amount of benzo(a)pyrene administered varied by a factor of 400. At 24 hours after dosing, from 1 to pmoles of ^{14}C was found bound to lung macromolecules regardless of the dose administered. These data suggest that linear extrapolation from high dose studies to environmentally relevant concentrations of inhaled materials would tend to underestimate the lung burdens of benzo(a)pyrene and thus, potential health risks. [Research supported by the Office of Health and Environmental Research, U.S. Department of Energy under Contract No. DE-AC04-76EV01013.]

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TOXICOKINETICS OF INHALED PURE AND PARTICLE-ASSOCIATED ORGANIC CHEMICALS. J.A. Bond, J.D. Sun, M.A. Medinsky, C.E. Mitchell, R.K. Wolff, and R.O. McClellan, Lovelace Inhalation Toxicology Research Institute, Albuquerque, NM-87185

Classes of organic compounds such as polycyclic aromatic hydrocarbons (PAH), nitro-PAH, aromatic amines, and azaarenes have been detected in emissions associated with energy production and use. These chemicals are associated with respirable particles and many have known mutagenic, carcinogenic, and/or toxic properties. There is a paucity of data on the fate, target organs, and potential human health risks associated with inhalation exposure of these chemicals. Toxicokinetic data have been obtained for inhaled benzo[a]pyrene, nitropyrene, aminoanthracene, and phenanthridone both in pure forms and associated with carbonaceous, organic, and inorganic particles. Rats were exposed by nose-only inhalation to aerosols of the different chemicals. Following each exposure, rats were sacrificed at various times and tissues were removed for analysis of parent compound and metabolites. In all cases, the rate of clearance of material from the respiratory tract occurred in two phases, an initial rapid phase and a subsequent slower phase. In general, when the chemical was inhaled in pure form, over 99% of the inhaled material was rapidly cleared with a half-time of less than 1 day. However, when the chemical was inhaled on particulate matter a significant fraction of the inhaled chemical was retained in the lungs (up to 50%) and this fraction cleared with a half-time of > 1 day (i.e. 1-30 days). The data obtained for the different chemicals have been used to predict lung concentrations of the inhaled chemicals in humans. Equilibrium lung burdens were predicted for humans using the animal toxicokinetic data and hypothetical exposure conditions (3.5 ng particles/L air, 8 hr/day, 0.1% PAH coating). The rate constants used for each calculation were taken from the toxicokinetic studies. The data indicate that chemicals coated on particless yield equilibrium lung burdens up to 1000 times higher than from exposure to pure aerosols of PAH. In summary, the results from these series of studies have shown that particle association of chemicals influences the rate of clearance of those chemicals. The data predict that under some conditions (e.g. particle association) lungs can accumulate significant quantities of inhaled chemicals. [Research performed under DOE Contract No. DE-AC04-76EV01013.]

SIGNIFICANCE OF THE EXTRAALVEOLAR PERIVASCULAR SHEATH IN THE ALVEOLAR CLEARANCE OF INSOLUBLE PARTICLES - S. Takenaka, H. Muhle, B. Bellmann and U. Mohr, Fraunhofer Institut fuer Toxikologie und Aerosolforschung, Hannover, FRG.

Previous inhalation studies on the localization of insoluble particles in the alveolar regions showed frequent deposition of the particles in the perivascular space of small blood vessels. It was suggested that the particles were at least in part translocated to the lung-associated lymph nodes after having entered the extraalveolar perivascular sheath.

In this experiment we compared the alveolar distribution of 5 types of insoluble particles inhaled at various concentrations by rats. (Fly ash from coal fired power plants, TiO2-anatase, TiO2-rutil, plastic powder, iron powder; 1 to 20 mg/m3, 3-12 months exposure).

We found frequent deposition of particles in the extraalveolar perivascular sheath in every group exposed to concentrations higher than 5 mg/m3. In addition, particle-laden alveolar macrophages had sometimes aggregated in the alveolar lumen, especially near the perivascular space and subpleural regions. At concentrations lower than 2 mg/m3, particle deposition rarely occurred in the perivascular space. However, slight accumulation of particles was always observed in the peribronchial lymphatic tissues and the lung-associated lymph nodes.

These findings confirm that the extraalveolar perivascular sheath plays an important role in the alveolar clearance of insoluble particles inhaled at high concentrations. At lower concentrations it is difficult to obtain morphological evidence for the alveolar clearance route, however, it cannot be excluded that the particles are also cleared via the perivascular space to the lung-associated lymph nodes.

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ACCUMULATION OF ETHOXYACETIC ACID DURING REPEATED EXPOSURES TO THE ETHYL ETHERS OF ETHYLENE GLYCOL AND ETHYLENE GLYCOL ACETATE. - H. Veulemans, D. Groeseneken, R. Masschelein, E. Van Vlem, Department of Occupational Medicine, Cath. University of Louvain, B-3000 Louvain, Belgium.

Ethoxyacetic acid (EAA) was found to be a major urinary metabolite of both the ethyl ether of ethylene glycol (EGEE) and of ethylene glycol acetate (EGEE-Ac) in short-term experimental exposures of humans. Because of its relatively long biological half-life (22-25 h) in these experiments, it was believed that this metabolite could accumulate during repeated exposures. This was investigated in a group of 5 women with daily occupational exposure to EGEE and EGEE-Ac.
Individual exposures were monitored per shift-halves and urine samples were taken before and after shifts during 2 observation periods of resp. 5 and 7 days. The daily exposures were fairly constant with an overall mean value of 14 mg/m^3 (sum of EGEE and EGEE-Ac in equivalent amounts of EGEE). Urinary EAA excretions showed a clear increase during the work week. Elimination during the weekends was far from complete and even after a prolonged period without exposures (12 days), traces of the metabolite were still detectable in urine (1.2 - 2.6 mg/g creatinine). Maxima at the end of a complete working week were estimated at 150 $\pm$ 35 mg EAA/g creatinine for average full-shift exposures to 19 mg/m^3 EGEE or 27 mg/m^3 EGEE-Ac.

INTERSPECIES COMPARISONS OF PULMONARY RESPONSES TO INHALED PARTICLES AND FIBERS: IMPLICATIONS FOR TOXICOLOGIC EVALUATIONS - DB Warheit, MS Stefaniak, and MA Hartsky, Du Pont - Haskell Lab., Newark, DE, USA.

Some of the major challenges for inhalation toxicologists involve the extrapolation of animal data to humans and to define the mechanisms of particle-induced lung toxicity. This is a difficult task, in part because interspecies differences abound, both in the lung as well as in other organs. Since toxicologic testing frequently requires utilization of several species, it would be useful to make interspecies comparisons of inhaled particulates under identical experimental conditions. Accordingly, we are investigating the lung responses of different rodent species to standard inhaled doses of either asbestos or carbonyl iron (CI) particles. Additionally, in vitro morphologic and functional studies were carried out on pulmonary macrophages (PM) recovered by bronchoalveolar lavage to complement the in vivo inhalation studies.

Rats and mice were exposed to aerosols of chrysotile asbestos for 1-3 hr (10 mg/m^3). In addition, 2 strains of rats, 3 strains of mice, and 1 strain each of hamsters and guinea pigs were exposed to aerosolized carbonyl iron particles for 1,3, or 6 hrs at 100 mg/m^3. Scanning electron microscopy of dissected lung tissue revealed that asbestos fibers and carbonyl iron particles deposited preferentially on alveolar duct bifurcations regardless of the species. Decreased numbers of particles were counted on bifurcations of guinea pigs compared to rats and mice. Time course studies showed that increased numbers of rat PM migrated to sites of particle deposition ($p<0.05$) and this correlated with an enhanced percentage of phagocytic macrophages following recovery by lavage ($p<0.01$). In vitro functional studies demonstrated that mouse PM phagocytic rates were depressed compared to the other 3 species. The results of chemotaxis studies demonstrated that PM in both rat strains migrated well to zymosan and CI activated sera ($p<0.001$) and lavage ($p<0.05$), while the other 3 species respond best to n-formyl peptides. Our data suggest that the rat is the most efficient model for clearing inhaled particles while hamsters and guinea pigs are more effective in clearing inhaled bacteria.

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FATE OF INHALED PARTICLES, DETERMINED BY NEUTRON ACTIVATION - A.P. Wehner, Battelle, Pacific Northwest Laboratories, Richland, WA 99352.

Pulmonary deposition, translocation and clearance of inhaled particles are important parameters in determining biological effects and health risks of air pollutants. Neutron activation provides a very sensitive technique to develop this information, which we have used to determine the fate of talc baby powder and fly ash in hamsters, Mount St. Helens volcanic ash in rats, and cigarette smoke in dogs. The rodent data are reviewed here.

Neutron activation produced radionuclides in the irradiated material, of which ^{46}Sc, ^{59}Fe, and ^{60}Co served as tracers. Rodents received single nose-only exposures to the irradiated dusts. Groups of four to six animals were serially sacrificed up to 4 months after exposure. Lungs, other tissues of interest, and excreta were subjected to γ-ray analysis. Detection limits were ~0.1 disintegrations/min, allowing detection of 10^{-11} g quantities of these elements. Analyzing for more than one radionuclide and comparing their ratios in the bulk dust to those in the tissues or excreta indicated whether a radionuclide represented particles in the tissue samples or had leached from the dust particle.

Six to 8% of inhaled talc was initially retained in the alveoli, with a biological half-life of 7 to 10 days. Alveolar clearance was essentially complete 4 months after exposure. No translocation of talc to liver, kidneys, ovaries, or other parts of the body was found. Picogram quantities of ^{60}Co found in the urine probably represented leached ^{60}Co. Two to 3% of inhaled fly ash was initially retained in the respiratory tract. Estimated biological half-lives were 3 and 35 days for airways and alveoli, respectively. After 99 days, the mean lung burden had decreased to ~10% of its initial value; extrapolation suggests near-complete pulmonary clearance at ~200 days after exposure. About 6% of inhaled volcanic ash was initially retained in the deep lung, with a biological half-life of 39 days. Mean lung burdens had decreased to ~20 and 10% of their initial values 90 and 128 days after exposure, respectively.

CONCENTRATION-TIME RELATIONS IN ACUTE INHALATION TOXICITY.
A THEORETICAL STUDY - A.L.M. Rutten, A. Zwart, P.G.J. Reuzel, TNO-CIVO Toxicology and Nutrition Institute, P.O. Box 360, 3700 AJ Zeist, the Netherlands.

Dose-response relations can be written as $Cexp^n.t$ = constant, which can be transformed to $P = b_0 + b_1 \ln Cexp + b_2 \ln t$, (equation 1), with: P = probit response; b_0, b_1, b_2 constants; $b_1/b_2 = n$; Cexp = exposure concentration; t = exposure time.
We considered theoretical models on distribution and working mechanisms of local and systemical acting agents to determine the range of values of n.

Local- (Agents acting on conductive airways and respiratory epithelium).
a. Agents acting on a location (loc) close to the source of exposure (nose, upper airways): C(loc) is almost immediately Cexp, and is independent of the exposure time; b_2 in equation 1 is 0 and $n = \infty$.
b. Agents acting on a location further away from the source of exposure (alveoli etc): $C(loc) = Cexp\ (1-e^{-kt}-e^{-lt}- \ldots)$ with k, l, ... constants. If k is the largest constant than n = 1 for $0<t<2k^{-1}$; n>1 for $t>2k^{-1}$ and $n = \infty$ for $t = \infty$.

Systemical- (Agents acting on a target organ (t.o)after having been transported by the blood circulation)
a. Exposed agent is acting agent.
$C(t.o) = Cexp\ (1-e^{-kt}-e^{-lt}- \ldots)$. Again if k is the largest constant n = 1 for $0<t<2k^{-1}$; n>1 for $t>2k^{-1}$ and $n = \infty$ for $t = \infty$.
b. Exposed agent is metabolised to an acting agent or causes enzyme deactivation.
- Metabolism or deactivation follows first order kinetics:
$\frac{dc}{dt} = \frac{Vm\ Cexp}{Km + Cexp}$ with Vm and Km constants. The amount of metabolite or of deactivated enzyme is / $Cexp\ (1-e^{-kt}-e^{-lt}- \ldots) = Cexp\ (t + k^{-1}e^{-kt} + l^{-1}e^{-lt} + \ldots) - Cexp$.
c. For $0<t<2k^{-1}$ $n = 2^{-1}$ and for $t>2k^{-1}$ $n = 1$, if k is the largest constant.
- Metabolism or deactivation follows zero order kinetics:
$\frac{dc}{dt} = Vm$
The amount of metabolite or of deactivated enzyme is independent of the exposure concentration; $b_1 = 0$ and $n = 0$.

Conclusions
- A value of n between 0 and ∞ is possible for both local and systemical acting agents.
- n is a function of the range of exposure times and will generally increase for the longer exposure periods for exposed agents that are acting agents.
- For exposed agents that are metabolised to acting agent or that cause deactivation of enzyme Habers rule (P = Cexp.t) with n = 1 can be applied for longer exposure periods.

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CATEGORY D
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INTERPRETATION OF EARLY LESIONS IN THE MOUSE LUNG: FIBROGENESIS AND TUMORIGENESIS H. P. Witschi, Oak Ridge National Laboratory, Biology Division, Oak Ridge TN 37831

In mouse lung, fibrosis (measured as an increase in total collagen) may develop following acute diffuse lung injury caused by such agents as butylated hydroxytoluene (BHT), bleomycin or cyclophosphamide. It is possible to amplify the fibrotic process by exposing BHT-damaged lungs to X-rays. Presumably, X-ray treatment interferes with repair of the alveolar epithelial lining, allowing fibroblasts to grow uninhibited. However, X-rays failed to potentiate fibrosis following exposure to bleomycin or cyclophosphamide. A reevaluation of cell kinetics following diffuse lung injury showed that it was possible to divide agents into two groups. BHT, methylcyclopentadienyl manganese tricarbonyl, $CdCl_2$ or oleic acid produced peak alveolar type II cell proliferation within 14 days. Cytostatic agents such as bleomycin, cyclophosphamide, BCNU or busulfan produced little cell proliferation. Moreover, alveolar type II cells only began to synthesize DNA 1 to 2 weeks following acute lung injury. It is possible that delayed reepithelization is responsible for the development of fibrosis seen after one single administration of these cytostatic agents.

Lung tumors are derived from type II alveolar cells or from Clara cells, depending on mouse strain. Certain carcinogens such as urethan produce cell hyperplasia whereas others such as 3-methylcholanthrene (MCA) fail to do so. Enhancement ("promotion") of lung tumor development also appears to be independent of cell proliferation. Repeated injections of BHT following a single dose of MCA will promote lung tumors even in the absence of all recognisable cell hyperplasia in the alveolar zone. On the other hand, hyperoxia (70% for 4 months) produces alveolar and bronchiolar hyperplasia and an increase in ornithine decarboxylase activity. The development of tumors is practically abolished. In conclusion, knowledge of cell kinetics in the lung may help on occasion to anticipate a certain pathologic response but also can be misleading in predicting long-term responses. (Operated by Martin Marietta Energy Systems, Inc. with U.S. Department of Energy.)

RELEVANCE TO MAN OF EXPERIMENTALY-INDUCED PULMONARY TUMOURS IN RATS AND HAMSTERS - U. Mohr and D.L. Dungworth, Hannover Medical School, Hannover, FRG and University of California, Davis, CA 95616.

Wide variations in incidence and types of pulmonary tumors among various species of animals are well recognized. In comparing human pulmonary tumors and those induced by respiratory tract exposure of rodents to chemicals, the focus has mainly been on differences in topographic distribution and histogenetic classification. Currently, four mechanistic aspects of pulmonary carcinogenesis are being explored which can help explain differences between human and experimentally-induced rodent tumors: 1) dosimetry of inhaled materials responsible for differences among animal species in anatomic sites of maximum local dose to epithelial cells; 2) variations in epithelial cell populations among species, particularly with respect to xenobiotic metabolism; 3) serial morphologic and functional correlations during carcinogenesis in vivo; and 4) studies of events leading to transformation of cultured cells in vitro. Comparative dosimetry and epithelial cell biology are considered elsewhere in this Symposium. This paper concentrates on information being developed from in vivo and in vitro carcinogenetic studies in rats or hamsters.

Activation of oncogenes and expression of their protein products are under intensive investigation as fundamental components of the set of carcinogenetic mechanisms. Studies of lung tumors induced in rats and mice by chronic inhalation of tetranitromethane reveal that the dominant transforming gene is a Ki-ras oncogene activated by mutation at the twelfth codon. This was the case irrespective of tumor type and host species. Since the Ki-ras oncogene appears so far to be the most important activated oncogene in human lung tumors, these findings provide preliminary evidence of the fundamental similarity of the rodent and human tumors. More important is to determine whether the sequence of oncogene activation and expression of products during the complex morphogenesis of lung tumors is similar in humans and animals.

Cell culture studies enable direct in vitro comparison of human and rodent cells and can provide quantitative data that can be used in scaling from the animal to man. Evidence to date indicates that fetal human broncho-alveologenic cells are less susceptible to toxic effects and DNA damage by the direct-acting carcinogen ethylnitrosourea. Culture conditions for comparing effects of indirect-acting carcinogens are being explored.

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A STUDY OF THE PATHOGENESIS OF EMPHYSEMA ASSOCIATED WITH LONG TERM NO_2 EXPOSURE - J.Kleinerman and M.P.C.Ip, Department of Pathology, Case Western Reserve University School of Medicine at Cleveland Metropolitan General Hospital, Cleveland, OH 44109

Current concepts of the pathogenesis of emphysema are based on the relative balance between elastolytic (E) and antielastolytic (AE) factors. In order to study the dynamic interactions during lung injury we have determined the quantitative change in (E) and (AE) forces in the alveolar lavage fluid of Syrian male hamsters following long term NO_2 continuous and intermittent exposure to NO_2 in concentrations of 30 ppm. The α_1 antielastase (α_1AE) and α_2 macroglobulin (α_2M) concentrations in alveolar fluid and in plasma and the neutrophil (N) and macrophage (M) concentrations in the alveolar fluid (AF) were determined during a continuous 12 month period NO_2 exposure. Studies were done at intervals of 1,3,7,10,14,21 and 30 days and at 3,6,9 and 12 month Plasma (P) and (AF) α_1AE and α_2M were determined by radio immunoassay (RIA). Total (N) elastase (EL) concentration was derived from the (EL) content of an aliquot of purified neutrophils and the total (N) content of the alveolar fluid at each sampling interval. The alveolar (α_1AE) and α_2M concentrations increased markedly within the first 24 hr of NO_2 exposure, as compared to controls (C) thereafter it decreased progressively with continuing exposure, until day 30 and thereafter, when it returned to control levels. The specific activity of the [α_1AE] is markedly depressed after the onset of NO_2, but increases to control values at 30 days. The (P) levels of α_1AE and α_2M during NO_2 show no significant changes from (C). The (N) and (M) content of the AF increases markedly within the first 14 days of NO_2. The (N) concentration returns to near control levels within 30 days, whereas alveolar (M)s decrease more gradually and remain at levels greater than control even after 12 months. Stoichiometric comparisons of the alveolar α_1AE and (N) elastase concentrations indicate an excess of antielastases at all times during the NO_2 exposure. This circumstance would minimize the destruction of alveolar elastin and limit the extent of the emphysema. This supports the pathologic and morphometric findings of minimal emphysema found in the lungs of the NO_2 exposed groups.

Similar studies were performed in hamsters exposed to a series of three intermittent exposures to NO_2 (30 ppm) for 7 days followed by removal from NO_2 for 14 days. The Stoichiometric comparisons of alveolar (AP and (N) elastases again indicate no excess of elastolytic activity at any time during or after the schedule of exposures.

These studies indicate the need to increase the elastolytic stimulus in the lung while simultaneously diminishing the antielastolytic activity in the design of an improved experimental model of human emphysema.

COMPARISONS OF RESPIRATORY FUNCTION RESPONSES OF LABORATORY ANIMALS AND MAN - J.L. Mauderly, Lovelace Inhalation Toxicology Research Institute, Albuquerque, NM 87185.

The respiratory function of man is measured in clinical, occupational and epidemiological settings to detect and characterize functional abnormalities and to follow the progress of lung disease. The pulmonary health of man is often described solely on the basis of measured function. Methods have been adapted so that function parameters measured in man can be measured in animals, including multiple indices of breathing patterns, lung volumes, parenchymal and airway mechanics, intrapulmonary gas distribution, alveolar-capillary gas exchange, pulmonary perfusion and blood gases. Specific techniques used for man and animals often differ, due primarily to the need for animal restraint and the inability to obtain voluntary, controlled respiratory movements from animals. However, tests of animals rarely need to be invasive beyond anesthesia, many can be performed without anesthesia, and all can be performed repeatedly. Because of differences in measurement technique and because the lungs of man and animals differ structurally, it is important to determine if measured functional responses to airway irritants and lung injury are similar in animals and man. Data on functional responses of man and animals to inhaled irritants, bronchoactive drugs, and pulmonary diseases (inflammation, emphysema and fibrosis) will be reviewed. Data from man and animals with radiation-induced pneumonitis and fibrosis and dust-induced pneumoconiosis will also be compared. This information indicates that similar lung injuries result in qualitatively similar alterations of respiratory function in man and laboratory animals, and that there are also many quantitative similarities. Respiratory function assays are a useful tool in inhalation toxicology as a response endpoint, to detect and characterize lung disease, to study morphologic-physiologic correlates and to place the results of animal studies in a context that can be extrapolated to man.. (Research supported by the Office of Health and Environmental Research, U.S. Department of Energy under Contract No. DE-AC04-76EV01013.)

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Datum, Unterschrift 9.Mai.87
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Datum, Unterschrift 9. Apr. 87

NASAL TUMOURS IN RATS AFTER SHORT-TERM EXPOSURE TO CYTOTOXIC CONCENTRATIONS OF FORMALDEHYDE VAPOUR - V.J. Feron, L.M. Appelman, R.A. Woutersen and J.P. Bruyntjes, TNO-CIVO Toxicology and Nutrition Institute, P.O. Box 360, 3700 AJ Zeist, The Netherlands

Formaldehyde vapour has been shown to be carcinogenic to rats and probably also to mice (Swenberg, J.A. et al., Cancer Res., 40, 1980, 3398; Albert, R.A. et al., J. Natl. Cancer Inst., 68, 1982, 597; Kerns, W.D. et al., Cancer Res., 43, 1983, 4382).
To study the chronic effects on the nose of exposure to clearly cytotoxic concentrations of formaldehyde during relatively short treatment periods, a long-term inhalation study was carried out in male rats using exposure levels of 0, 10, and 20 ppm and exposure periods of 1, 2 or 3 months (6 h/day, 5 days/week) followed by observation (non-exposure) periods of at most 29, 28 or 27 months, respectively. A total of 450 rats was used. Preliminary results indicate the occurrence of compound-related inflammatory, hyperplastic and metaplastic changes of the nasal respiratory epithelium even after a non-exposure period of 29 months. Grossly visible nasal tumours were not found. However, microscopic examinations carried out so far indicate the presence of a limited number of nasal tumours in rats of the high-concentration group.

A RAT MODEL OF PHYSIOLOGIC ADAPTATION TO OZONE (O_3) - D.L. Costa,* J.S. Tepper, M.J. Wiester,* J.R. Lehmann, M.F. Weber, S. Fitzgerald, M. Stevens, M.E. King. *Health Effects Research Laboratory, U.S.E.P.A., RTP, NC 2771; Northrop Services Inc., RTP, NC 27709.

Repeated daily exposure of humans to O_3 evokes lung dysfunction which subsides or "adapts" by the 3rd or 4th day of challenge. To investigate morphological and biochemical alterations which may be related to these functional changes, a rat model of adaptation was developed. Male, F-344 rats were exposed to 0.0, 0.35, 0.5, or 1.0 ppm O_3 for 2.25 hrs each of 5 consecutive days during which 8% CO_2 was superimposed for alternate 15 min periods to stimulate ventilation as does exercise in the human protocols. Observed concentration-dependent alterations in tidal breathing parameters were largely adapted by day 3 in the 0.35 and 0.5 ppm group, but were minimally attenuated at 1.0 ppm. In a second study, groups of rats were exposed to 0.0 or 0.5 ppm O_3 as above, but were not repeatedly monitored for functional changes. Instead, separate cohort groups were evaluated each day. Preliminary functional evaluations indicated less adaptation than previously observed, but this may reflect the use of cohort groups. Immediately postexposure the animals were killed and lungs were excised and weighed. The right lobe set was lavaged with sterile saline while the left lobe was fixed with 2% glutaraldehyde at 25 cm H_2O. Lavagate determinations included: albumin and glucose as permeability markers, cell counts and differentials, and α-1-antiproteinase (α1-Pi) function. Freely permeable urea was used to calculate the lung lining layer volume. Lavagable cell populations did not change, but macrophage phagocytosis was suppressed without evidence of "adaptability". Permeability, α1-Pi function and lung structure analyses are in progress. These data will be used to correlate physiologic "adaptation" to O_3 with underlying organic processes. This is an abstract of a proposed presentation and does not necessarily reflect EPA policy.

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CENTRIACINAR AIRWAY REMODELING IN RATS CHRONICALLY EXPOSED TO OZONE - D.M. Hyde, B.C. Barr, C.G. Plopper and D.L. Dungworth, California Primate Research Center, University of California, Davis, CA 95616.

The morphologic changes in the centriacinar region of lungs from 14 rats exposed to either filtered air (8) or 0.95 ppm ozone (6) eight hours daily for 90 days were analyzed using morphometry. Rats were killed with an overdose of sodium pentobarbital administered I.P., the trachea cannulated and thoracic viscera and lungs removed from the chest. Lungs were fixed via intratracheal instillation of a paraformaldehyde/glutaraldehyde cacodylate buffered fixative at 30 cm water pressure. Lung volumes were determined by weight displacement and the left lung lobe was sectioned transversely into 12 slabs. One random block was selected from each slab, and 12 blocks per rat were embedded in paraffin and studied by light microscopy. With these sections we estimated the volume of proximal bronchiole, the segment proximal to the terminal bronchiole, terminal bronchiole, respiratory bronchiole and alveolar duct and sac within the lung. Bronchioles dissected from pre-selected regions of the right middle lobe were studied by transmission electron microscopy. Dissected terminal airways were sectioned in a longitudinal plane through their mid-lumen. From these dissected airways, four subregions of the centriacinus were then examined: 1) terminal bronchiole, 2) respiratory bronchiole, 3) centriacinar alveolar duct wall and 4) centriacinar alveolar septa. The results of this study showed that following chronic ozone exposure there was a 13-21% decrease in luminal diameter and a 32% decrease in luminal volume of terminal bronchioles. The volume of proximal bronchiole was unchanged in volume. The most notable change was a 3.4-fold increase in respiratory bronchiole volume. While the walls of terminal and respiratory bronchioles were significantly thicker, the centriacinar alveolar duct wall was 90% thicker and showed a marked increase in cuboidal epithelial cells. The results indicate that respiratory bronchiole is formed from centriacinar alveolar duct following chronic exposure to ozone, and that the narrowing of terminal bronchioles at 30 cm of water pressure fixation may reflect decreased compliance of the bronchiolar wall.

Supported by NIEHS Grant P01 ES00628.

ROLE OF VITAMIN E IN THE DIFFERING RESPONSE TO NO_2 INJURY IN THE RAT AND THE HAMSTER - K. Miller, D. Baylcy and D.G. Walters, British Industrial Biological Research Association, Carshalton, Surrey, SM5 4DS, U.K.

Pulmonary surfactant may exercise a dual role both in maintaining alveolar stability and in protecting the respiratory membrane against the deleterious effects of lipid peroxidation and other toxic injury. We have shown previously that hamster and rat differ in their response to NO_2 exposure and that vitamin E is present in surfactant obtained from lavage fluid or whole lung homogenate in both species. Vitamin E levels were found to be appreciably higher in the rat than hamster and could thus play a role in protecting against NO_2 toxicity in the rat.

We have now investigated whether the two species differ in their ability to utilise vitamin E on animals maintained on diets supplemented with vitamin E (375mg/kg diet) for a 4 week acclimatization period prior to NO_2 exposure.

Administration of vitamin E supplemented diet increased both plasma concentration and the level of vitamin E present in whole lung in the rat. This effect differed from that obtained in the hamster where administration of vitamin E increased plasma concentration three-fold but had no effect on the level of vitamin E in whole lung surfactant. This suggests that in addition to higher levels of vitamin E in the plasma the rat may differ from the hamster in its ability to utilize vitamin E pools and transport them to other organs such as the lung. This might provide some explanation for the greater susceptibility of the hamster to the NO_2 injury.

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Datum, Unterschrift 2. Apr. 87
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Datum, Unterschrift 2.Apr.87

DOSIMETRIC CONSIDERATIONS FOR EXTRAPOLATING RESULTS OF RAT INHALATION STUDIES TO HUMANS: CADMIUM CARCINOGENICITY STUDIES AS AN EXAMPLE - G. Oberdörster, University of Rochester, Dept. of Biophysics, Rochester, NY 14642.

Interpretation of results from rat inhalation studies and extrapolation of those results to humans requires knowledge in both rats and humans about regional deposition efficiencies in the respiratory tract, pulmonary retention half times of the chemical in question, the metabolism of the compound in the respiratory system and the sites of action within the respiratory tract. Inhaled cadmium compounds have been shown to induce lung tumors in both rats and man, however, it appears that the tumorigenic effect is much greater in rats than in man. Tumors induced in rats by inhalation of cadmium seemed to be mostly of peripheral origin, whereas in humans inhaled cadmium induced mostly tumors of bronchogenic origin. Model deposition calculations were performed assuming an eight hr/day exposure to cadmium aerosols of different particle sizes, heterodispersity and concentrations. For a submicrometer size cadmium aerosol - the particle size used in rat studies - the deposited dose per unit surface area in the transitional region of the lung when inhaled via the nose is about 2 times higher in the rat than in man, whereas the surface area dose in the conducting airways of both species is about the same. Inhalation of a larger sized cadmium aerosol - often encountered under workplace conditions, e.g., exposure to CdO dust with a median particle size of 3µm - leads to a doubling of the surface area dose in the upper conducting airways of man. Mouth breathing increases the dose per unit surface area in generations 2-6 of the human lung significantly by an additional factor of five to six. Since pulmonary retention of Cd differs significantly between rats (T 1/2 = 80 days) and primates (T 1/2 = 770 days) this has also to be considered for long-term accumulation of Cd in the lung. Respective model calculations show that the accumulated dose of Cd per g of lung tissue is greater in man by a factor of two to five. However, the dose rate per g of lung tissue during cadmium aerosol exposure is more than fourfold greater in the rat. These results demonstrate that differences in the sites of tumor induction between rats and humans by inhaled cadmium may be due to differences in the surface area dose and the dose rate. Such dosimetric differences should be considered when designing inhalation experiments in rats and extrapolating the results to humans.

CAN ANIMAL DATA RELATE TO HUMAN BRONCOGENIC EFFECTS?

J.N. Pritchard and A. Black

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Despite the strong epidemiological evidence linking cigarette smoking to bronchogenic carcinoma, it has proved very difficult to reproduce this effect in laboratory animals. This suggests that the response of laboratory animals may be a poor indicator of risk to the human bronchial region. As there is evidence to suggest that the site of deposition is related to the site of origin of tumours, this probably reflects a different pattern of deposition in the animals. This paper will discuss the factors that may be responsible for differences in deposition between humans and animals. In particular, the effects of deposition in the upper airways and residence time in the lung will be considered, using the deposition of cigarette smoke as an example. The behaviour of volatile and hygroscopic materials will be discussed in this context.

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Datum, Unterschrift 9.Apr.87 Rg

The NTP/NIEHS STUDIES ON METHYL ISOCYANATE - J.R. Bucher, E.E. McConnell, B.A. Schwetz, M.D. Shelby, National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709.

Prior to the December, 1984, release of methyl isocyanate (MIC) in Bhopal, India, few toxicologic studies had been performed on MIC, and the human health consequences for the exposed population were unknown. Because of this, the U.S. National Toxicology Program, and National Institute of Environmental Health Sciences performed studies with rats and mice to characterize respiratory injury and to assess the potential for systemic toxicity through histopathologic studies and assessments of immune, reproductive and genetic effects. MIC inhalation in single 2-hour exposures, or in repeated, 6-hour exposures over 4 days, resulted in immediate and delayed deaths, both attributed to respiratory distress. Immediate deaths were associated with sloughing of the epithelium of the respiratory tract to the level of the bronchioles. In survivors, the nasal mucosae rapidly healed, but small airways remained occluded with mucus, fibrin, desquamated cells and fibropepithelial scars. Function studies demonstrated severe-persistent obstructive lung disease with secondary complications of pulmonary hypertension and cardiac arrhythmias. However, little evidence of direct systemic effects was found. MIC-exposed mice showed transient decreases in bone marrow cellularity and hematopoietic progenitor cells, but no functional deficits in host resistance to bacterial, viral or malarial challange were seen. Exposure during late pregnancy resulted in increased fetal and neonatal deaths, but no evidence of reduced fertility or teratogenic effects was found. Results of in vitro and in vivo genetic toxicity assays were mixed and the conclusion that MIC is weakly genotoxic was based primarily on increases in chromosomal aberrations and sister chromatid exchanges both in cultured mammalian cells and in bone marrow of exposed mice. Despite the fact that the exposures in these animal studies were to pure MIC, whereas the Bhopal exposures presumably were to MIC and various reaction products, these experimental findings are quite consistent with published reports of the medical conditions of survivors of the Bhopal disaster.

EARLY RESPONSE OF THE SURFACTANT AND ANTIOXIDANT SYSTEMS IN RAT LUNGS AFTER CADMIUM CHLORIDE INHALATION.

J Boudreau, R. Vincent, D. Nadeau*, B. Trottier, M. Fournier, K. Krzystyniak and G. Chevalier, Université du Québec à Montréal, QC, Canada, H3C 3P8 and *Université de Sherbrooke, QC, Canada, J1K 2R1.

We are developing an animal model for assessing the early effects of inhaled pollutants on the lungs in terms of sensitive and specific biochemical parameters. Male Long-Evans rats were exposed to a $CdCl_2$ aerosol ($5mg/m^3$) for 1 hr and were sacrificed at 1, 4, 8, and 16 days after treatment. The toxicity was assessed by studying the responses of the tissue antioxidant defence and the pulmonary surfactant (SF) systems. Pulmonary edema (wet/dry wt) was observed only on day 1. The total activities of superoxide dismustase (SOD), glutathione reductase (GR) and glucose-6-phosphate dehydrogenase (G6PD) in the lung homogenates (HOM) increased (125%-250%; $p<0.05$; n=8) throughout the study. Significant increases in the specific activities (U/mg protein or dry wt) of G6PD were observed on days 1 and 4, suggesting an oxidative stress. The general increases in GR and SOD total activities seemed associated with the infiltration by inflammatory cells, as indicated by the increased levels of acid phosphatase and B-N-acetylglucosaminidase. The response of the SF system was monitored by assaying the alkaline phosphatase activity (AKP) and the phospholipid (PL) content in HOM and cell-free bronchoalveolar lavages (BAL). The AKP activity in the HOM decreased (30%) on day 1, while no activity could be detected in the BAL, indicating an inhibition of AKP by Cd. The recovery of PL in the BAL decreased by 44% on day 1 although the lung PL content increased by 61%, suggesting an alteration in SF secretion. On day 4, the high recovery of PL in the BAL (312%) may reflect a reduced recycling and/or increased secretion of extracellular SF. Also, the important changes in the AKP specific activity (U/mg PL) observed on days 4 (42% decrease), 8 (262% increase), and 16 (38% decrease) were interpreted as an indication of qualitative changes in extracellular SF. Cadmium intoxication appears to alter significantly the pulmonary SF system and to produce an oxidative stress. The AKP activity is particularly sensitive to Cd, and may possibly provide an early and sensitive indicator of SF alterations. (Supported by NSERC and IRSSTQ).

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Bestätigung der Übereinstimmung mit dem Original
Datum, Unterschrift 9.Mai.87

EFFECTS OF A "NUISANCE" DUST INHALATION ON LAVAGABLE LUNG CELLS - O. Creutzenberg, B. Bellmann, M. Ocak and H. Muhle, Fraunhofer-Institut für Toxikologie und Aerosolforschung, Hannover, FRG.

Particles for which no specific toxic effects are known are classified as "nuisance" dusts. A general threshold limit value has been established for an occupational exposure to those aerosols amounting to 6 mg/m^3 in Germany and 5 mg/m^3 in the U.S. respectively.
The aim of the study was to investigate effects of a long-term exposure to nuisance dusts. In addition to lung clearance measurements, the functions of the alveolar leucocytes were studied. Three dusts were tested in parallel. Test materials were titanium dioxide, polyvinyl chloride powder (PVC) and iron powder at aerosol concentrations of 3.2, 8 and 20 mg/m^3. The exposure lasted up to 8 months. The used animals were female Fischer rats. Ten animals of each concentration group were taken for lung lavage. Lavagable lung cells were examined for the following parameters: total cell number, cell viability, phagocytic activity, adherence and chemotaxis tests, peroxidase staining and differential cell counting. The results showed an almost constant number of total cells over all groups except the highest PVC concentration group, the cell number of which increased significantly. The number of polymorphonuclear cells increased from low to higher concentrations. The results indicate more pronounced effects by PVC powder compared to TiO_2 and Fe dust. Previous experiments during exposure of the animals have shown that PVC reduces alveolar lung clearance. The relevance of these effects for the general threshold limit value for dusts will be discussed.

METHYL ISOCYANATE (MIC) TOXICITY IN RATS AND GUINEA PIGS FOLLOWING ACUTE, HIGH CONCENTRATION EXPOSURE - D.E. Dodd, M.R. Fedde, E.H. Fowler, C.M. Troup, L.A. Maginniss, and F.R. Frank, Bushy Run Research Center, Union Carbide Corporation, Export, PA 15632

Early reports from India indicated that humans were dying within minutes to a few hours from exposure to MIC. To examine the probable causes of these rapid mortalities, studies involving rats and guinea pigs focused primarily on the consequences of acute pulmonary damage. All MIC inhalation exposures were acute, of short duration (mainly 15 min.), and high in concentration (ranging from 25 to 3500 ppm). The MIC vapor exposures were statically-generated in a double chamber design. Guinea pigs were more susceptible than rats to exposure-related early mortality. A greater than one order of magnitude difference was observed between an MIC concentration that caused no early mortality in rats (3506 ppm) and an MIC concentration that caused partial (6%) early mortality in guinea pigs (225 ppm) for exposures of 10 to 15 min. duration. Although rat and guinea pig packed erythrocytes exposed in vitro to 100, 500, 1000, or 2000 ppm of MIC vapor had a concentration-related inhibition of cholinesterase activity, in vivo exposure to 1000 ppm of MIC did not result in inhibition of erythrocyte cholinesterase activity. Also, no direct effects of MIC on hemoglobin function were observed in guinea pigs exposed to 700 ppm for 15 min. However, blood O_2 affinity was reduced due to severe metabolic acid-base disturbances (lactic acidosis). Guinea pigs exposed to MIC at concentrations of 240 to 628 ppm had a marked reduction in PaO_2 and pHa and an elevated tracheal pressure during artificial ventilation. The low PaO_2 was only slightly elevated when the animals were ventilated with 100% O_2. Thus, MIC inhalation caused severe pulmonary blood shunting and ventilation/perfusion imbalance. This, in turn, led to hypoxemia, metabolic acidosis, and tissue hypoxia, which could produce death. The pulmonary gas exchange deficit presumably resulted from sloughing of large sheets of conducting airway epithelium and mucus production resulting in plugging of major airways. Exposure-related degenerative changes were also seen in the alveolar epithelium and the endothelium in both rats and guinea pigs. However, the guinea pig was considerably more sensitive to MIC vapor.

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EICOSANOID PRODUCTION BY RABBIT ALVEOLAR MACROPHAGES AFTER IN VITRO AND IN VIVO OZONE EXPOSURE - K.E. Driscoll and R.B. Schlesinger, Institute of Environmental Medicine, New York University Medical Center, NY, NY 10016.

This study was designed to examine the effect of ozone on alveolar macrophage (AM) eicosanoid biosynthesis and to compare the responses observed using in vitro and in vivo exposure techniques. AM were obtained from New Zealand White rabbits by bronchoalveolar lavage, established in monolayer culture, and exposed for 2 hr to atmospheres containing 0.0, 0.1, 0.3, or 1.2 ppm ozone. The AM were maintained in culture for 6 hr post exposure, the conditioned media harvested, and analyzed for the presence of PGE2, PGF2 α, PGF1α thromboxane, LTB4 and LTC4 using radioimmunoassay. For the in vivo exposure study, groups of 5 rabbits were given a single 2 hr exposure to air, 0.1, or 1.2 ppm ozone and sacrificed immediately or 24 hr post exposure. AM lavaged from the exposed rabbits were cultured for 6 hr and the conditioned media analyzed for eicosanoids. In vitro exposure to ozone resulted in a significant increase in PGE2 and, to a lesser extent, PGF2α production at both the 0.3 and 1.2 ppm levels; no significant changes in PGF1α production were observed for any of the ozone concentrations. LTB4, LTC4 and thromboxane could not be detected after ozone exposure. Regression analysis of the in vitro exposure PGE2 and PGF2 α data demonstrated a significant linear concentration-response relationship with the slope of the PGE2 regression being significantly greater than that of PGF2 α. Preincubation of AM with 10 µg/ml indomethacin inhibited prostaglandin synthesis after in vitro ozone exposure. In vivo exposure to 1.2 ppm resulted in significantly increased quantities of PGE2 and PGF2 α released at both the immediate and 24 hr sacrifice points. After in vivo exposure to 0.1 ppm, no change in prostaglandin production was observed. These results demonstrate that both in vitro and in vivo ozone exposure stimulates eicosanoid production by rabbit AM. The responses observed using the two exposure techniques were qualitatively similar, with quantitative differences likely due to the higher effective ozone dose which would be expected using the in vitro system. Increased production of prostanoids (particularly PGE2) may affect respiratory defense mechanisms. PGE2 is known to down-regulate the functional activities of macrophages and other immune effector cells. Increased levels of this prostanoid in the alveolar region represents a potential mechanism for the impaired pulmonary defenses which have been observed after ozone exposure.

MORPHOGENESIS OF THE LUNG CANCER INDUCED BY DIESEL EMISSION - S.Kitamura,Y.Takaki,N.Kuwabara and Y.Fukuda,Juntendo University School of Medicine,Hongo,Bunkyo-ku,Tokyo,Japan.

In order to observe the carcinogenesis of diesel emission, long-term inhalation studies were carried out on SPF F-344 rats (4 week of age) using a heavy-duty (11 liter) and light-duty (1.8 liter) diesel engin.Each exhaust gas was diluted to five levels concentration. A group of rats consisted of 120 males and 120 females for each level of exhaust gas concentration. Rats were exposed 16 hours/day, 6 days /week for up to 30 months to exhaust gas. The experimental rats were kept microbiologically so clean and the rats showed no evidence of bacterial infection of respiratory organ.

Histolgicaly,the diesel particles were deposited in the interstitial tissue and phgocytosed by alveolar macrophages along with alveolar septum.These changes were dependent on the duration of exposure and the exhaust gas concentration. Hyperplasia of the type II alveolar epithelial cells and bronchiolar epithelium was increased with varying degrees of anthracosis.This hyperplasia was a focal and scattered lesion until 12 months inhalation.However,over 18 months inhalation,those hyperplastic lesions extened to the adjacent alveolar spaces and fused with the other focal lesions turning into a diffuse pattern. In such diffuse hyperplastic lesion,there was papillary and solid epithelial proliferation with slight cellular atypia without nodular formation or compression of the adjacent tissue. Some of these findings were difficult to differentiate from adenoma and occasionally even the carcinoma.Over 24 months,squamous metaplasia was often observed in subpleural hyperplastic lesion with focal interstitial fibrosis.

The incidence of primary lung tumors including adenoma, carcinoma and other tumors was dependent on heavy-duty diesel engin.However, the incidence was independent on light-duty diesel engin. The majority of these tumors were squamous cell carcinoma and adenosquamous carcinoma. Pure adenocarcinoma was few in number.

It can be concluded that morphogenesis of the lung cancer which is induced by diesel emission is related to hyperplasia and squamous metaplasia of bronchiolar-alveolar epithelial cells as precursorous changes.

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Datum, Unterschrift 9. Apr. 87

THE EFFECT OF DUST INHALATION ON BACTERIAL CLEARANCE FROM THE LUNG - M.I. Gilmour, F.G.R. Taylor and C.M. Wathes
School of Veterinary Science, University of Bristol, Langford House, Langford, Bristol, BS18 7DU, England.

Exposure to airborne dust may compromise the respiratory defences of farm livestock by blocking non-specific and specific clearance mechanisms, thus predisposing to opportunistic and primary pathogens. To test this hypothesis we are examining the clearance of a bacterial infection, and the immune response to that infection, during exposure to airborne dust.

We have developed a model of respiratory infection in the mouse using Pasteurella haemolytica. Mice are subjected to various concentrations of an inorganic dust, titanium dioxide, and infected with P. haemolytica by aerosol. The bacterial clearance, specific serum antibody and lymphocyte sensitivity to Pasteurella antigen are monitored during two weeks post-infection.

Prior exposure to airborne dust impaired bacterial clearance. The effects on the immune response subsequent to infection will be discussed. We conclude that dust particles of a respirable size adversely affect clearance mechanisms, and that the effect is dose-related.

COMPARISON OF RESPIRATORY FUNCTIONS IN FISCHER 344 AND WISTAR RATS - U. Heinrich and A. Wilhelm, Fraunhofer-Institut für Toxikologie und Aerosolforschung, Hannover, FRG

Various strains of Fischer 344 and Wistar rats have been used in basic research and toxicological tests of all designs and it is well known that these two strains differ in some biological data, e.g. growth rate, clinical chemistry, hematology, spontaneous tumors a.o.
In inhalation toxicology, lung function measurements are often used to assess toxic effects of inhaled material on pulmonary mechanics and diffusion. But, so far, there are no investigations comparing normal lung function of Fisher 344 and Wistar rats.
Therefore, we started to measure various lung functions (mechanics and diffusion) in groups of female Wistar [Han: WIST] and Fischer [CDF (F-344) CrlBR] rats using the whole-body plethysmograph and halothane anesthetised animals breathing spontaneously through a transorally inserted tracheal cannula. Spontaneous breathing-related lung mechanics, maximum flow-volume- and quasistatic lung pressure-volume relationships, subdivisions of lung volume and CO diffusing capacity were measured. The animals were investigated at the age of approx. 4, 13 and 18 months.
The most striking difference between these two strains of rats was the significantly higher lung volume of the 18 weeks old Wistar rats compared to the 17 weeks old Fischer rats, both having a mean body weight of 220 g. This difference in the lung volume was even more pronounced approx. 1 year later, although, the mean body weight of both strains of rats had increased by 50%. But, only the size of the lung and not the mechanical property appeared to be different because lung compliance and resistance normalized to functional residual capacity was very similar in Fischer and Wistar rats.

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Datum, Unterschrift 9.Apr.87

ELECTRON MICROSCOPIC STUDIES ON RAT LUNGS AFTER PROLONGED EXPOSURE TO DIESEL ENGINE EXHAUST, A.KATO, S.ISHIWATA, (HERP), Japan Automobile Research Institute, Inc., Yatabe, Tsukuba-gun, Ibaraki, Japan.

Inhalation experiments on diesel engine exhaust were performed for 30 months using F344 rats. The results of electron microscopic observations (TEM.SEM) on the respiratory organs are reported here.

In the particle-containing groups, the main changes of the airway surface (SEM) during the 30 months of inhalation were irregularity, shortening or loss of cilia of the ciliated epithelia, and irregularly arranged protrusion or hypertrophic foci of the non-ciliated epithelia. The changes of the cilia were prominent in the trachea or main bronchi, however, the changes of the non-ciliated cells were perdominantly focused on the Clara cells of more the distal regions of the airways.

In the alveoli (TEM), acceleration of phagocytotic activity at the surface of type I epithelia and uptake of particles into the attenuated cytoplasm were noticed. Proliferation of hypertrophic type II epithelia was noted with increased microvilli and swollen or fused lamella inclusion bodies. Slight increase of collagen fibers, edematous swelling and carbon laden macrophages in the interstitium of the alveolar walls were seen occasionally. In the alveolar lumen, macrophages and laminated materials discharged from the type II epithelia were observed. These changes in the airways and alveoli were more prominent at the high dose groups of both the LD and HD series. These lesions also increased slightly with the lengths of inhalation time. On the other hand, the particle influence experiment gave rise to a similar extent of lesions both in the particle-containing and the corresponding particle-free groups. Thus, the lesions of the airway epithelia seemed to be caused mainly by the effects of gaseous components.

Finally, electron microscopic morphometry showed a dose-dependent increase of the arithmetic mean thickness of the air-blood barrier only in the groups in the LD series after inhalation for 6 and 12 months. However, after 30 months of inhalation, some groups showed marked variations in alveolar wall thickness, due to infiltration of leukemic cells into the interstitium and slight fibrosis. Therefore, it was difficult to differentiate the changes caused by diesel emissions.

NASAL TUMOURS IN RATS AFTER SEVERE INJURY TO THE NASAL MUCOSA AND EXPOSURE TO FORMALDEHYDE VAPOUR - V.J. Feron, H.R. Immel, L.M. Appelman, R.A. Woutersen and A. Zwart, TNO-CIVO Toxicology and Nutrition Institute P.O. Box 360, 3700 AJ Zeist, The Netherlands

Prolonged exposure to formaldehyde vapour may induce nasal tumours in rats (Swenberg, J.A. et al., Cancer Res., 40, 1980, 3398; Albert, R.A. et al., J. Natl. Cancer Inst., 68, 1982, 597) and probably also in mice (Kerns, W.D. et al., Cancer Res., 43, 1983, 4382). To study the significance of damage inflicted upon the nasal mucosa for the induction of nasal tumours by formaldehyde, a long-term inhalation study was carried out in which male rats with a severely damaged (by electrocoagulation) or undamaged nasal mucosa were exposed to 0, 0.1, 1.0 or 10 ppm formaldehyde vapour for 6 h/day, 5 days/week during a period of 30 months, or a period of 3 months followed by a non-exposure period of 27 months. The total number of rats was 880. Preliminary results suggest that chronic exposure of rats to 1 or 10 ppm formaldehyde leads to a higher incidence of nasal carcinomas in rats with a damaged nasal mucosa than in rats with an intact nasal mucosa.

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Datum, Unterschrift 2.Mai.87

USE OF BRONCHOALVEOLAR LAVAGE TO ASSESS THE TOXICITY OF AIRBORNE MATERIALS - R. F. Henderson and R. O. McClellan, Lovelace Inhalation Toxicology Research Institute, Albuquerque, NM 87185

The epithelial lining fluid (ELF) of the respiratory tract is the first substance encountered by inhaled materials. Analysis of this fluid and the cells associated with it can be used to detect the initial response of the respiratory tract to the inhaled material. ELF can be sampled by bronchoalveolar lavage (BAL). This technique has proven useful in three areas of toxicologic research: 1) BAL can be used to detect an acute inflammatory response in the bronchoalveolar region. This approach has been used to rank the pulmonary toxicity of a series of compounds (for example, a series of nickel salts) and to determine the amount of a material in the lung required to elicit an inflammatory response. 2) BAL can be used to follow the progress of a lung injury sequentially to determine if the initial inflammatory response leads to normal repair or to chronic inflammation and development of irreversible lung pathology. It has been used in this manner to determine if the acute response of the lung to inhaled particles is predictive of the long-term effect of the particles retained in the lung. 3) BAL can be used to elucidate the pathogenesis of various pulmonary diseases. Analysis of ELF for parameters such as mediators of inflammation, growth factors, protease/antiprotease balances has been an aid in determining the processes by which lung pathology develops. Advantages of BAL are that it is quantitative, allows detection of early changes in the respiratory tract, it can be done serially, and it is integrative in that it detects inflammation at any point in the luminal portion of the bronchoalveolar region. Disadvantages are that it is an invasive procedure and results are not site specific. BAL represents a valuable additional tool by which one can assess the response of the respiratory tract to inhaled toxins and is complementary to established methods such as histopathology, radiology, and pulmonary function assessment. [Research performed under U.S. Department of Energy Contract No. DE-AC04-76EV01013.]

THE LARYNX AS A POTENTIAL TARGET ORGAN IN AEROSOL INHALATION STUDIES ON RATS - D.R. Klonne, R.H. Garman, W.M. Snellings, D.E. Dodd, and B. Ballantyne, Bushy Run Research Center, Export, PA 15632.

The larynx has been observed to be a target organ for the particulate fraction, but not for the vapor phase, of cigarette smoke (Coggins et al., Toxicol. 16:83, 1980). In conducting 2-, 4-, and 13-week liquid aerosol inhalation studies (6 hr/day; MMAD ≤ 4.5 μ) on an aqueous silane solution (gamma-methacryloxypropyltrimethoxysilane), laryngeal granulomas were produced in F-344 rats after as few as 9 exposures to a mean aerosol concentration of 50 mg/m^3. Rats exposed to vapors of the same material for 9 exposures at mean concentrations up to 426 mg/m^3 exhibited no laryngeal toxicity. In neither aerosol nor vapor studies was there an indication of lung toxicity. In the 4-wk aerosol study, scanning electron microscopy (EM)/ energy dispersive X-ray analysis evaluations confirmed the presence of siliceous spheres of approximately 2 μ in diameter in the submucosa of the larynx. The laryngeal granulomas appeared as a polypoid protrusion of the overlying mucosa into the lumen of the airway. The siliceous spheres were often surrounded by large numbers of epithelioid histiocytes with smaller numbers of giant cells also present. Transmission EM analysis indicated that the siliceous spheres were present in the cytoplasm of squamous mucosal cells, within histiocytes and fibroblasts in the submucosa, and extracellularly in the submucosa. The size of the granuloma remained nearly constant in rats allowed a 13-wk non-exposure recovery following 13 weeks of exposure at concentrations ranging from 50 to 244 mg/m^3.

Guidelines (TSCA, FIFRA, OECD) for subchronic inhalation aerosol studies do not specifically require that the larynx be histologically evaluated. Furthermore, the site of the lesion appears to be quite specific, occurring posterior to the epiglottis in the ventral portion of the larynx at the level of the vocal cords and immediately adjacent to the ventral laryngeal diverticulum. Because of the serial sections required to achieve the specific site, a single random section through the larynx would often miss a lesion unless it were quite large. The results of these studies raise the question of whether the larynx is a potential target organ for aerosols of silane compounds, or for many aerosol test compounds, because of an unusual cellular sensitivity or an increased deposition and/or decreased clearance of particles in this area in the rat..

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SUBCHRONIC INHALATION STUDY OF PIGMENTED POLYMER IN RATS - H. Muhle[1], U. Mohr[1], S. Takenaka[1], W. Koch[1], R. Fuhst[1], R. Kilpper[2], and R. Mermelstein[2]

1. Fraunhofer-Institut fur Toxikologie and Aerosolforschung, Hannover 61, F.R.G.,

2. Joseph C. Wilson Center for Technology, Xerox Corporation, Rochester, New York, 14644, U.S.A.

As part of a long-term investigation, a subchronic inhalation study of a pigmented polymer fraction was conducted by exposure of groups of SPF F-344 rats for six hours/day, five days/week for 13 weeks. The test material is a special 9600-type xerographic toner enriched about 10-fold in respirable size particles such that it is about 35% respirable according to ACGIH criteria. The nominal aerosol exposure concentrations were 0, 1.0, 4.0, 16.0 and 64.0 mg/m^3.

The animals tolerated the exposure conditions well; no unscheduled deaths occurred. Body weight, clinical chemistry values, food consumption and organ weights were normal with the exceptions noted for the highest exposure group. Constant body weight and clinical chemistry values, slight decrease in food consumption and about 50% increase in lung weight were observed in the highest exposure group.

Histopathological examination of the lungs indicated a dose related increase of particle accumulation and macrophage recruitment. A very slight degree of septal thickening of the alveolar structure was noted in the highest exposure groups.

LONG-TERM INHALATION STUDY WITH HAMSTERS AND MICE USING VARIOUS CADMIUM COMPOUNDS - U. Heinrich, R. Fuhst, H. König, L. Peters and S. Takenaka, Fraunhofer-Institut für Toxikologie und Aerosolforschung, Hannover, FRG

Inhalation of 12.5, 25 and 50 µg cadmium/m^3 in $CdCl_2$ for about 150 hrs/week for 18 months induced lung carcinomas in rats (Takenaka et al. 1983). Therefore, the carcinogenic effect of $CdCl_2$ and three other Cd-compounds ($CdSO_4$, CdO, CdS) and the susceptibility of other species (hamsters, mice) merited investigation. In this experiment, male and female Syrian golden hamsters and female mice (NMRI) were exposed to aerosols of four different Cd-compounds on 5 days/week, for 19 hrs/day or 8 hrs/day for 12 - 16 months. After termination of the exposure, the animals were kept in clean air for another 6 - 12 months. The Cd-exposure was terminated prematurely if there was a substantial loss of body weight or increased mortality. The preliminary results of this experiment are:
After exposure to the different Cd-compounds for approx. one year followed by a clean air period of almost another year at the most, no neoplastic alterations in the respiratory tract of the hamsters have been observed up to now. The spontaneous lung-tumor rate in the lungs of the control mice was about 32 % after an experimental time of two years. No additional tumor-inducing or inhibiting effect could be observed after Cd-exposure.
Additionally, the Cd-content of the lung, liver and kidney was determined and correlated to the experimental time.

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Datum, Unterschrift 2.Apr.87

ENDOGENOUS LIPID PNEUMONIA INDUCED BY METHYLNAPHTHALENE, A COMBUSTION GAS OF KEROSINE, IN $C_6B_3F_1$ MICE

Y. Konishi*, Y. Emi*, T. Taki**, Y. Murata* and Y. Yokose*
*Department of Oncological Pathology, Cancer Center, Nara Medical College and **Department of Biochemistry, Shizuoka College of Pharmacy

Methylnaphthalene is a complex of α- and ß-isomer and exists as a contaminant in combustion gas of kerosine. We found that endogenous lipid pneumonia was induced by painting methylnaphthalene twice weekly on shaved skin on the backs of female $B_6C_3F_1$ mice. Endogenous lipid pneumonia developed in 3/11 mice (27%) and 16/16 mice (100%) given 59.7 mg/kg body weight methylnaphthalene for 61 and 105 weeks, respectively, and in 31/32 mice (97%) given 118.8 mg/kg for 61 weeks. Serial killing study showed that the requirement of times and doses for 100% induction of the pneumonia was 30 weeks and a total of 7128 mg methylnaphthalene in mice given 118.8 mg/kg and 20 weeks and a total of 9504 mg in mice given 237.6 mg/kg body weight.

Histopathologically, the pneumonia was characterized by swelling and proliferation of alveolar type-II cells, foam cell accumulation, the appearance of cholesterol crystals and thickening of alveolar interstitial spaces. Electronmicroscopically, the number and size of lamellar bodies in swollen and proliferating type-II cells were increased and foam cells contained degenerated lamellar bodies. Free lamellar bodies in the alveoli were also observed. Biochemically, cholesterol and dipalmitoylphosphatidylcholin and minor phospholipid increased in the lung with the pneumonia. The phospholipid was purified and identified as phosphatidylglycerol.

These results give important information for understanding the underlying mechanisms of endogenous lipid pneumonia in mice.

MODIFICATION OF LUNG TUMOR GROWTH BY HYPEROXIA - R.C. Lindenschmidt* and H.P. Witschi; Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831. *Present address: Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, OH 45247

Recent work in this laboratory showed that continuous exposure of mice to an atmosphere of 70% oxygen inhibited the development of lung tumors initiated by a pulmonary carcinogen. In the present work, the effects of hyperoxia on lung tumor development were examined further in mice and also in a second species, rats. Male A/J mice were injected intraperitoneally with various doses of the carcinogen urethan or 3-methylcholanthrene (3-MCA) and 4 days later placed into chambers containing either 21% O_2 (air control) or 70% O_2 until sacrifice 4 months later. Exposure to 70% O_2 significantly inhibited the development of urethan or 3-MCA-induced lung tumors at all dose levels. A potential mechanism of action of hyperoxia on lung tumors, interference in DNA synthesis, was investigated using *in vivo* autoradiography. Oxygen (70%) did not inhibit the incorporation of thymidine into the DNA of mouse lung tumor cells. Hyperoxia and tumor inhibition studies were conducted in a second species. Male F344 rats were treated with a single intratracheal instillation of 3-MCA and 1 week later were exposed to air, 40% or 70% O_2 for 7 weeks. Rats kept in air developed multiple lung lesions identified as keratinized squamous carcinomas. Hyperoxia (both 40% or 70% O_2) significantly reduced both tumor multiplicity and tumor incidence. No differences were found in the histologic appearance of the tumors in the treated and control rats. It is concluded that hyperoxia can inhibit development of transformed cells *in vivo* in the lungs of two species, mice and rats. It appears that this inhibition is not the result of interference with DNA synthesis. (Oper. by the Martin Marietta Energy Systems, Inc. with USDOE. RCL supported by the post graduate research training program administered by Oak Ridge Associated Universities for the U.S. Department of Energy.)

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EFFECT OF A "NUISANCE" DUST INHALATION ON IMMUNOLOGIC FUNCTIONS OF RAT ALVEOLAR MACROPHAGES - M.-L. Lohmann-Matthes and H. Muhle, Fraunhofer-Institut für Toxikologie und Aerosolforschung, Hannover, FRG.

Particles for which no specific toxic effects are known are classified as "nuisance" dusts. A general threshold limit value has been established for an occupational exposure.
Test material were titanium dioxide, polyvinyl chloride powder (PVC) and iron powder at aerosol concentrations of 3, 8 and 20 mg/m^3. The exposure lasted up to 8 months. Alveolar macrophages from rats exposed to either dust or control air were tested for the following parameters: Production of tumor necrosis factor, spontaneous and activated extracellular cytotoxicity against tumor targets, spontaneous and activated intracellular cytotoxicity against Leishmania microorganisms. High concentrations of PVC exposure resulted in a preactivation of alveolar macrophages documented in all assay systems. In addition an elevated susceptibility for further activation was consistently observed with these macrophages.
In contrast high dosage exposure of iron powder resulted in a significant suppression of macrophages functions which was most pronounced in the extracellular tumor cell killing. The relevance of these results will be discussed.

CARCINOGENICITY OF DIESEL EXHAUST INHALED CHRONICALLY BY RATS - J.L. Mauderly, R.K. Jones, W.C. Griffith, R.F. Henderson and R.O. McClellan, Lovelace Inhalation Toxicology Research Institute, Albuquerque, NM 87185.

The finding of mutagenic activity in diesel exhaust soot led to concern for potential carcinogenesis in man. A chronic inhalation bioassay was performed in the rat to determine if diesel exhaust could be a pulmonary carcinogen. Male and female F344/Crl rats were exposed 7 hr/day, 5 day/wk for up to 30 mo, beginning at 4 mo of age to automotive diesel engine exhaust at soot concentrations of 0.35, 3.5 or 7.0 mg/m^3 or sham exposed to clean air. Exhaust was generated by 1980 5.7 L Oldsmobile engines operated on the Federal Test Procedure Cycle and burning certification fuel. Rats were sacrificed at 6 mo intervals to measure lung burdens of diesel soot and for histopathology. Other rats either died or were sacrificed after 30 mo of exposure. Lungs were fixed, sectioned into 3 mm slices and examined by dissecting microscope to detect tumors. Lesions were stained and examined by light microscopy. Survival and body weight were unaffected by exposure. Exhaust exposure did not affect body weight or survival. Other than soot accumulation, no adverse health effects were observed at the lowest exposure level. Focal fibrotic and proliferative lung disease accompanied a progressive accumulation of soot in the lung at the two highest exposure levels. After 24 mo of exposure, 20.8, 11.5 and 0.6 mg of soot were present in lungs of rats at the high, medium and low exposure levels, respectively. The prevalence of lung tumors was significantly increased at the high (13%) and medium (4%) dose levels above the control prevalence (1%). Four tumor types, all of epithelial origin, were observed: adenoma; adenocarcinoma; squamous cyst; and squamous cell carcinoma. Tumors occurred late during the exposures; 81% were observed after 24 mo. Logistic regression modeling demonstrated a significant relationship between tumor prevalence and both exposure concentration and soot lung burden. These results demonstrate that diesel exhaust, inhaled chronically at a high concentration, is a pulmonary carcinogen in the rat. (Research supported by the Office of Health and Environmental Research, U.S. Department of Energy, under Contract No. DE-AC04-76EV01013.)

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RELATIVE EFFECTS OF INHALED NITROGEN DIOXIDE AND DIESEL EXHAUST IN ADULT RATS AND RATS WITH DEVELOPING LUNGS - J.L. Mauderly, D.E. Bice, N.A. Gillett, R.F. Henderson, J.A. Pickrell and R.K. Wolff, Lovelace Inhalation Toxicology Research Institute, Albuquerque, NM 87185.

There is concern that infants and children might be more sensitive than adults to the effects of inhaled toxicants. In this study, the pulmonary effects of inhaled nitrogen dioxide (NO_2) and diesel exhaust (DE) in rats exposed as adults were compared to effects in rats exposed during lung development. Rats were exposed 7 hrs/day, 5 days/wk for 6 mo to NO_2 at 9.5 ppm, DE at 3.5 mg/m^3 soot, or to clean air as controls. Two age groups were studied; rats exposed beginning at 6 mo of age (adults) and rats exposed beginning at birth (young). Evaluations after the 6 mo exposure included respiratory function, airway fluid enzymes and cytology, pulmonary immune responses, lung tissue collagen and proteinases, histopathology, clearance of radiolabeled particles, and lung burdens of DE soot. NO_2 reduced body weight and altered airway fluids of both groups, but increased lung weight only in adults. DE altered airway fluid parameters and lung collagen and proteinases of both groups, but increased the number of cells in pulmonary lymph nodes and slowed particle clearance only adults. Lung burdens of soot were similar in both groups at the end of exposure, but the distribution of soot differed. Soot-laden alveolar macrophages formed focal aggregates in adults, but were scattered in young rats. Soot cleared from the lung more rapidly after the end of exposure in young rats than in adults. These results indicate that rats are not more sensitive to inhaled NO_2 or DE during lung development than during adulthood. These findings also suggest that the response of macrophages to inhaled soot particles is different in adult and developing rat lungs. The results of this study suggest that there might not be a need to consider infants and children as a special risk group for inhaled environmental pollutants.
(Research performed in facilities provided by the Office of Health and Environmental Research, U.S. Department of Energy with funds provided under Agreement 83-13-2 with The Health Effects Institute.)

EARLY DISTRIBUTION OF AN INHALED RADIOAEROSOL IN RATS - A.N. Payne, I.W. Lees, M.J.S. Gazeley, P.M. Webbon & G.E. Woolley, Dept. of Mediator Pharmacology, Wellcome Research Laboratories, Beckenham, Kent. BR3 3BS; Central Analytical Laboratories, (Biological), The Wellcome Foundation Limited, Dartford, Kent. DA1 5AH; and Depts. of Medicine, and Surgery, The Royal Veterinary College Field Site, North Mymms, Hatfield, Herts. AL9 7TA

We have used a simple and generally applicable isotopic method to compare the relative anatomical deposition and early distribution of aerosolised particles following head-only exposure of either conscious or anaesthetised rats.

Conscious or anaesthetised (Inactin 75mg kg^{-1} i.p.) male Wistar strain rats (235-265g) were exposed for 10 min to a radioaerosol of distilled water containing a tracer amount (0.3 mCi ml^{-1}) of ^{99m}Technicium pertechnate. The aerosol was generated by a Turnet jet-nebuliser driven by compressed air (14 p.s.i., flow rate 4L min^{-1}) delivering approximately 0.2 ml min^{-1}. The aerosol particle size distribution ranged from 0.7 - 15µm (mode 0.9µm, weight mean diameter of 9µm). At the end of the exposure period each animal was sacrificed with CO_2. The head, thorax and stomach regions were scanned for radioemission. Further readings were also taken from dissected tissues. (Table 1).

Table 1 Regional γ-radioemission (c sec^{-1}), energy peak 139-140 KeV.

Field/Tissue	Conscious	% Total	Anaesthetised	% Total
Head	1116 ± 206	36.8	724 ± 53	73.6
Thorax	380 ± 73	12.8	135 ± 26	13.8
Trachea	32 ± 15	1.1	15 ± 9	..6
Lungs	134 ± 44	4.5	60 ± 9	6.2
Oesophagus	135 ± 18	4.5	5 ± 2	0.6
Stomach -	1169 ± 621	38.6	26 ± 19	3.0
Duodenum	29 ± 20	1.0	5 ± 1	0.5
Heart	28 ± 11	1.0	6 ± 2	0.7

All values represent the mean (± s.e. mean) result from 5 animals in each group.

In conscious animals, relatively little deposition and subsequent retention of radioaerosol mass occurred in the lower respiratory tract (LRT) compared with either the head region or the gastrointestinal tract (GIT). In anaesthetised animals, there was a very marked reduction in radiomission from the GIT coupled with an increase in the proportion of radioaerosol retained in the head region. The most obvious explanation for this is a depression of the swallowing reflex.

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CHRONIC EFFECTS FOLLOWING LONG-TERM EXPOSURE TO GASOLINE ENGINE EXHAUST IN RODENTS - U. Heinrich, L. Peters, and B. Bellmann, Fraunhofer-Institut für Toxikologie und Aerosolforschung, Hannover FRG.

Long-term studies with diesel engine exhausts have shown several chronic-toxic effects mainly in the respiratory tract of the experimental animals. Nowadays, however, at least in Europe about 90 % of automobiles burn leaded gasoline without catalytic converters. It, therefore, also seemed essential to investigate the possible chronic-toxic effects of gasoline engine exhaust in a long-term animal inhalation experiment.
Rats and hamsters were exposed to gasoline engine exhaust for 19 hrs/day, 5 days/week for up to 2 years. The exhaust was generated by a VW engine running on the US-72 driving cycle. The engine was operated with a leaded European reference fuel. The exhaust was diluted with clean air in ratios of about 1:60 and 1:30. The mean lifetime of the animals was not affected by the exposure. Only the rats exposed to the less diluted exhaust showed a lower body weight gain than the controls. Wet and dry weights of the lungs and hearts of both species increased slightly. Lead content was enriched in blood and bone in correlation to that of the exposure atmospheres. Clinical-chemical, haematological, biochemical and cytological investigations primarily showed some CO-induced changes in both species, mainly in the 1:30 exposure groups. Some of the exposure-related effects appeared to be reversible 6 months after termination of the exposure. After two years of exposure the respiratory tract, being the main target organ in inhalation experiments, showed predominantly in the rats a deterioration of the alveolar lung clearance and altered mechanical lung functions such as increased airway resistance and decreased lung compliance.

THE ROLE OF COMPLEMENT IN THE EARLY PATHOGENESIS OF ASBESTOSIS - DB Warheit, LH Overby, and AR Brody. Du Pont-Haskell Lab , Newark, DE and NIEHS, North Carolina, USA.

Asbestosis is a lung disease clearly associated with occupational and environmental exposure to inhaled asbestos fibers. The pathogenesis of this disease has not been well established. Pulmonary macrophages have been proposed as the connecting link between fiber-induced inflammation and the develpment of pulmonary fibrosis.
In experimental studies using rats and mice, we have previously shown that pulmonary macrophages migrate to sites of asbestos deposition to form a component of an early lesion. Here we report that inhaled asbestos fibers activate a complement-dependent chemoattractant thus recruiting macrophages to sites of fiber deposition, and facilitating the earliest lesions of asbestosis. To support this conclusion, inhalation studies were carried out where normal and decomplemented (CVF-treated) rats as well as congenic strains of C5-normal ($C5^+$) and C5-deficient ($C5^-$) mice were exposed to chrysotile asbestos. In addition, in vitro studies using pulmonary macrophage chemotaxis as a bioassay for complement activation were utilized. Our data showed that incubation of asbestos fibers with rat serum or normal lavaged lung progeins produced a substantial chemotactic response ($p<0.01$). Moreover, proteins lavaged from the lungs of asbestos-exposed rats produced significant chemotactic activity when compared to sham-exposed controls ($p<0.01$). To investigate the role of complement in facilitating the macrophage recruitment response, $C5^+$ and $C5^-$ mice, as well as normal and CVF-treated (cobra venom factor) rats were exposed to chrysotile asbestos for brief periods and the macrophage response was quantified by scanning electron microscopy (SEM). The numbers of accumulated macrophages were significantly decreased in the $C5^-$ mice and CVF-treated rats ($p<0.01$). Time course studies showed that chemotactic factor elaboration preceded the macrophage migration response ($p<0.01$). SEM x-ray spectroscopy revealed that decreased percentages of macrophages from CVF-treated, exposed rats phagocytized fibers. We conclude that complement activation by the inhaled fibers plays an important role in the early development of asbestosis.

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Datum, Unterschrift 9.4.87

CELL-TO-CELL AND CELL-TO-FIBER INTERACTIONS IN ASBESTOS-INDUCED LUNG DISEASE - KE Pinkerton & RR Mercer, University of California, Davis, CA and Duke University, Durham, NC.

Although the mechanisms by which asbestos fibers cause disease are not known, it appears that certain interactions between pulmonary cells and fibers are important. Recent work suggests that the accumulation and retention of asbestos in the pulmonary interstitium plays a key role in the genesis of fibrosis. However, movement of fibers to the interstitium and those cells involved in the translocation and subsequent events leading to fibrosis are not well understood. To address these questions morphometric methods and computer-assisted three-dimensional imaging were used to visualize and quantify these phenomena in the lungs of rats exposed by inhalation to chrysotile asbestos for up to 12 months. Of particular interest were associations of epithelial and inflammatory cells with mesenchymal cells in the presence of asbestos fibers. Epithelial transport of fibers was found to be literally an extracellular event. Passage of fibers via membrane-lined channels through intact viable epithelial cells was noted with one end of the fiber in the airspace and the other end in the interstitium. Once fibers gained access to the interstitial compartment, an intense cellular response was elicited consisting of fibroblasts, monocytes and macrophages. Three dimensional imaging of interstitial cells demonstrated a close apposition of monocytes and macrophages to fibroblasts with numerous plasma membrane contacts between these cells. Increased collagen deposition was commonly noted surrounding these cell masses. Multiple cells acting upon a single fiber were common with portions of a fiber contained in an epithelial cell and interstitial macrophage or fibroblast. Macrophages were the only cells containing extracellular pockets in which portions of asbestos fibers had become coated with calcium phosphate deposits. These findings suggest that the epithelium plays an important role in the movement of respired fibers to the interstitium. The response of the interstitium to the presence of asbestos consists of numerous cell contacts between fibroblasts, macrophages and monocytes subsequent to collagen deposition. The importance of these cell-to-cell communications and cell-to fiber interactions are likely to be central to the genesis of asbestos-induced lung disease.

DEGENERATIVE, INFLAMMATORY, AND PROLIFERATIVE LESIONS OF THE NASAL MUCOSA OF RATS AND MICE EXPOSED BY CHRONIC INHALATION TO SELECTED ORGANIC CHEMICALS WITH POTENTIAL FOR HUMAN OCCUPATIONAL EXPOSURE - R.A. Renne, R.A. Miller, W.E. Giddens, Battelle Northwest Laboratories, Richland, WA 99352, G.A. Boorman and R.R. Maronpot, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709.

Several industrially important organic chemicals were selected by the National Toxicology Program for carcinogenicity/toxicity assays by chronic inhalation exposure. Groups of 50 Fischer 344/N rats and B6C3F1 mice of each sex were exposed in inhalation chambers to one of two or three concentrations of the test chemical for 6 hours per day, five days per week for up to 103 weeks. Rats and mice developed a wide spectrum of lesions in the nasal mucosa in response to inhalation exposure to these chemicals. Inhalation of propylene oxide induced epithelial tumors, hyperplasia, squamous metaplasia, and chronic rhinitis in rats and primary vascular tumors in the nasal mucosa of mice. Propylene induced nasal epithelial hyperplasia and squamous metaplasia in rats. Methyl methacrylate induced rhinitis and olfactory epithelial degeneration in rats and mice. 1,2-epoxybutane induced nasal epithelial tumors in rats and epithelial hyperplasia, squamous metaplasia, degeneration, and inflammation in rats and mice. 1,3-butadiene induced chronic rhinitis, osseous and cartilaginous metaplasia, and olfactory epithelial degeneration in mice. The morphology of these induced lesions will be described, illustrated, and compared with nasal lesions reported by other investigators in rodent inhalation toxicity and carcinogenesis studies.

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Datum, Unterschrift 9.Apr.87

LONG-TERM INHALATION STUDIES ON EFFECT OF EXHAUST FROM HEAVY AND LIGHT DUTY DIESEL ENGINS ON F-344 RATS - Y.Takaki, S.Kitamura,N.Kuwabara and Y.Fukuda,Juntendo University School of Medicine,Hongo,Bunkyo-ku,Tokyo,Japan.

In order to observe the carcinogenesis of diesel emission, long-term inhalation studies were carried out on SPF F-344 rats(4 weeks of age) using a heavy-duty(11 liter) and light-duty(1.8 liter) diesel engin.Each exhaust gas was diluted to five levels concentration,and was supplied to each inhalation chamber in the barrier.A group of rats consisted of 120 males and 120 females for each level of exhaust gas concentration.Rats were sacrified at 6,12,18,24 and 30 months.In addition,an experiment for observing the influences of particle was carried out using diluted and filtered exhaust gas in which particles of exhaust had been removed.
Histopathological examination revealed during 30 months of inhalation,swelling and hyperplasia of type-II alveolar epithelial cells surrounding the particle,hyperplasia of bronchiolar epithelia toward peripheral air space.These changes were found in the lungs after 6 months exposure.The number of the foci and the extent were increased in relation to the duration of exposure and the exhaust gas concentration.The incidence of primary lung tumors including adenoma,carcinoma and other tumors was dependent on heavy-duty diesel engin.However,the incidence was independent on light-duty diesel engin.
In the study of the filtered exhaust gas,there was no difference of histological changes of the lung from those of the control group.
Leukemia,breast tumor and other tumors were not signficantly increased in the experimental group as well as the control group following 30 months inhalation.

HYALURONIC ACID IN BRONCHOALVEOLAR LAVAGE; A MARKER OF FIBROTIC DEVELOPMENT IN QUARTZ-EXPOSED RATS? - G. Tornling, A. Eklund, G. Unge and R. Hernbrand, Department of Thoracic Medicine and Department of Clinical Chemistry, Karolinska Hospital, S-104 01 Stockholm, Sweden.

The level of hyaluronic acid (HA), a connective tissue component, in bronchoalveolar lavage fluid (BAL) is correlated to decreased lung volumes in sarcoidosis. In order to investigate whether hyaluronic acid could be a marker of fibrosis in another interstitial lung disease, silicosis, we measured the level of HA in BAL fluid from rats exposed to silica by intratracheal instillation. Three animals were exposed to 40 mg crystalline silica containing 98 % quartz with a mean diameter of 1.2 um. Three animals were exposed to 40 mg amorphous silicon dioxide with crystalline components less than 1 % and with a mean diameter of 0.05 um. One rat was sham injected with physiological saline. The total number of recovered alveolar cells was increased in the rats exposed to crystalline silica. There was a marked increase in the proportions of neutrophils and lymphocytes. The level of HA was higher in the quartz-exposed rats (mean 54 ug/l) than in the animals exposed to amorphous silicon dioxide (mean 7 ug/l) and the sham injected rat (2 ug/l). Microscopic evaluation of the lungs revealed massive pulmonary fibrosis in the quartz-exposed rats but not in the other animals. Thus, the level of HA in BAL fluid in rats exposed to crystalline silica seems to be a possible marker of fibrotic development.

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AGE-DEPENDENT CHANGES AND NON-NEOPLASTIC SURFACE PROTRUSIONS IN THE LARYNGEAL AND TRACHEAL EPITHELIUM OF THE SYRIAN GOLDEN HAMSTER (MESOCRICETUS AURATUS) - C. Bröckmeyer and U. Heinrich, Fraunhofer-Institut für Toxikologie und Aerosolforschung, Nikolai-Fuchs-Str. 1, 3000 Hannover 61, FRG

The interior of the larynx and trachea of 8, 12.5 and 17-month-old hamsters was examined using scanning electron microscopy. Some of the specimens were successively embedded in Epon and investigated in semithin sections by light microscopy. Between the 8th and 17th months of life, simple metaplasia and slow mucus cell hyperplasia occurred in the hamster tracheae. Whilst an increase in mucus cells occurred between the cartilaginous rings, simple metaplasia was conspicuous in the surrounding large patches of unciliated cells, which covered the tracheal cartilages in the young hamsters. Flat or dome-shaped cells with microvilli covered the glottis and supraglottis of the 8-month-old hamsters where ciliated cells were rare. The vocal cords were covered by flat cells with microfolds and microridges. The older hamsters showed the same form of surface differentiation in the false fold area also.

Although no tumors were present, three types of surface protrusion were visible: (1) slow projections of tracheal mucosa caused by submucosal calcifications; (2) variously formed aggregations of mucus which protruded from mucus glands; and (3) papillary hyperplasia of the vocal cord mucosa.

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2484
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Datum, Unterschrift 9.Apr.87 Rg

POPULATION STUDIES IN RISK ASSESSMENT: STRENGTHS AND WEAKNESSES - Margaret R. Becklake, McGill University, Montreal, Quebec. Canada.

Epidemiologic studies provide information on the distribution and determinants of health related events in populations. Use is made of whatever method or study design (prevalence, case control, cohort) is appropriate to the health related event in question, depending amongst other things on its nature, incubation time, and the certainty with which it is possible to establish a diagnosis. Exposure response relationships make an important contribution to establishing causality particularly when an environmental agent is under scrutiny. Applicability of the findings to risk assessment and to environmental standard setting, in the workplace or in the public health context, is directly related to the extent to which the environmental measurements used to characterize exposure are quantitative rather than qualitative.

Asbestos is a topical example to illustrate the strengths and weaknesses of population based information in this context. It is also one responsible for malignant as well as nonmalignant illhealth effects, thus challenging both molecular and experimental biology (to explain mechanisms) and epidemiology (to quantitative risk). For this agent, too, the epidemiologic data base is probably more extensive than for any other. Its major strength (and this is true for any population data base) is biologic: human data does not require account to be taken of species differences. In addition, many occupational exposures have been reasonably well characterized in terms of airbrone fibres or dust, and they usually involve definable populations whose health status can be directly assessed. Sample size, when limited to a particular workforce, may reduce sensitivity. Nevertheless workplace standards, reasonably broadly based, have been framed around the risk of developing pulmonary fibrosis (asbestosis). A weakness of the data base is its insensitivity at low levels of exposure. Nevertheless because there is almost no epidemiologic data on the health consequences to the general public of environmental exposure, eg. in schools or building, extrapolations from the occupational data base have been used for risk assessment to the public, the major concern being cancer. Alternative strategies, also epidemiologic, are however available for assessing the impact on the public's health, for instance monitoring sex trends in mesothelioma incidence, and these might also provide an approach to risk assessment.

HUMAN CLINICAL EXPOSURE STUDIES: BODY BOX OR PANDORA'S BOX - M.J. Utell, University of Rochester Medical Center, Rochester, NY 14642

Controlled clinical studies have provided a means for examining responses to air pollutants identified from epidemiologic studies. Typically, the exposures are performed in environmental chambers and the responses are assessed by indices of respiratory mechanics. To date, inhalation studies have identified general patterns of lung function response in specific subpopulations. Several observations from clinical studies will be discussed to illustrate the relevance of these findings. For example: 1) after inhalation of ozone, normal and asthmatics manifest equivalent reductions in lung volumes at similar pollutant concentrations. 2) With acute exposure to the soluble gas SO_2 or acidic sulfate particles, asthmatics may be an order of magnitude more sensitive than healthy adults and characteristically show changes in flow rates and airway resistance. 3) In contrast, following inhalation of the oxidant NO_2, responses have been less consistent and more difficult to characterize but have included both obstructive and restrictive changes in volunteers with underlying airways disease. In order to examine mechanisms of pollutant-induced toxicity, the technique of bronchoalveolar lavage has been introduced into controlled clinical studies. Endpoints studied to date have included influx of inflammatory cells, measurements of products of arachidonic acid metabolism, analysis of proteins and enzymes released by alveolar macrophages, and lavaged leukocyte antiviral activity. Recently, other approaches available in the clinical arena including nasal lavages and clearance rates of radiolabelled aerosols from the airway to the blood have been adapted to evaluate pollutant responses. Although the clinical study cannot monitor the development of chronic disease from exposure, data from the "body box" has impacted substantially on our understanding of acute pollutant-induced effects. Further efforts to characterize subpopulations at risk and examine mechanisms of response using pulmonary data from controlled pollutant studies are clearly warranted.

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Datum, Unterschrift 9.Mai.87 Rq

OCCUPATIONAL EXPOSURE STANDARDS IN EUROPE: HISTORY, PRESENT STATUS AND FUTURE TRENDS -

D. Henschler, Institute of Toxicology, University of Würzburg, Fed. Rep. Germany

The first exposure standards were published in Germany as early as 1886 by K.L. Lehmann. By 1938, more than 100 short- and long-term standards had been proposed. At present, Germany, the Netherlands and Sweden prepare their own lists of standards; some other countries who up to now have used the US TLV-List are now starting initiatives of their own. Although the legislative background differs widely, all lists have important general features in common: separation of scientific evaluation from political decisions; consideration of field experience as well as animal experimentation; handling of carcinogens as a special category; preparation of monographs to elucidate the background for setting individual standards.

The establishment of occupational exposure standards is based on the assumption that thresholds of toxic effects do exist. Some model cases to demonstrate the existence of a threshold have been published. Prerequisites for thresholds are: reversibility of the relevant toxic effect; reversal of the toxic effect must have zero order kinetics; on repeated exposure, a steady-state level of the occupational toxicant must be reached which is regarded as safe; sufficient knowledge about the mechanism of action must be available. Most standards are, however, based on insufficient empirical information. At present, new philosophies are being elaborated to create "safe" standards for some types of occupational carcinogens.

During the past two decades, some new entries into the lists of standards have been made: classification of occupational carcinogens, regulations for peak vs. time-weighted average exposures, applicability or inapplicability of standards for women of child-bearing age. Recently, the EEC has again tried to establish a common list for the European member states.

CURRENT APPROACHES FOR DETERMINING WORK PLACE EXPOSURE LIMITS IN THE USA -

T.R. Lewis, National Institute for Occupational Safety and Health, Cincinnati, OH 45226

Application of research findings to the development and support of work place exposure limits for chemical substances in the United States of America is performed by several organizations -- the Occupational Safety and Health Administration (OSHA), the Mine Health and Safety Administration (MSHA), the National Institute for Occupational Safety and Health (NIOSH), the American Conference of Governmental Industrial Hygienists (ACGIH), the American National Standards Institute (ANSI), the American Society for Testing and Materials (ASTM), the American Industrial Hygiene Association (AIHA) and individual states. It is the function of OSHA and MSHA to promulgate legal standards. NIOSH has responsibility for developing criteria and making recommendations to OSHA and MSHA for the promulgation of legal standards. Individual states also promulgate standards which are legal within their respective jurisdictions. Recommendations by the other organizations, are not legally binding, but are often voluntarily assumed by industry and may be adopted as legal standards by regulatory agencies. Industries, in turn, also develop work place exposure limits for application to their particular facilities; this is particularly important when an industry is the sole manufacturer or user.

By contrast to certifying food additives, drugs and pesticides, there are no formalized testing requirements for determining the hazards from chemical substances used within the work environment. However, the key question to be addressed in determining occupational exposure limits is what levels pose significant hazards to health and what levels can be accepted without undue risk to health. Development of occupational exposure limits involves review and evaluation of available technical information on a chemical substance and publication of written documentation supporting a proposed exposure limit which then may be adopted by a sponsoring professional organization (ACGIH, AIHA, ANSI, ASTM) or promulgated into law by regulatory agencies.

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Datum, Unterschrift 2.Apr.87

CORRELATION OF CARCINOGENIC POTENCY ESTIMATED FROM ANIMAL AND HUMAN DATA - K.S. Crump, B.A. Allen, A.M. Shipp, K S Crump and Company/Clement Associates, Inc., Ruston, LA 71270

This study provides a detailed and systematic investigation of the correlation between estimates of carcinogenic potency derived from animal and human data. Chemicals included are all those for which suitable animal and human data could be located and for which there are strong indications that the chemical is carcinogenic in either animals or humans. Twenty-three chemicals were found to satisfy these criteria; these include thirteen industrial chemicals (for which exposures are primarily via inhalation), seven drugs, two food additives or contaminants, and tobacco smoke. The human data on each of these chemicals were used to calculate a carcinogenic potency and a corresponding range. The animal data were entered into a computer data base that permitted a wide range of analyses to be performed systematically. The analyses performed to date indicate a strong correlation between the animal and human results. These correlations are strongest when analyses are restricted to the higher quality animal data. These results indicate that estimates of human cancer risk can be reasonably based on animal data. They also provide information on the uncertainty in such estimates and on the most appropriate ways to extrapolate animal data to humans. The analysis approach that most nearly approximates that used by the U.S. Environmental Protection Agency appears generally to overestimate risk in humans from the chemicals in this analysis by about sevenfold.

OZONE REMOVAL IN THE NASOPHARYNX AND LUNGS OF NORMAL MAN DURING TIDAL BREATHING - J.J. O'Neil, T.A. Gerrity, R.A. Weaver, J.H. Berntsen, J.H. Overton, and F.J. Miller, Inhalation Toxicology Division, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, School of Public Health, University of North Carolina, Chapel Hill, NC 27514, and Environmenal Monitoring Services, Inc., Chapel Hill, NC 27514.

The purpose of this study was to determine the amount of ozone removed in the nasopharynx and lungs of normal volunteers in order to better estimate the actual dose of ozone delivered to pulmonary tissues. Respiratory gases in 18 young non-smoking male subjects were collected from the posterior pharynx through a French #8 polyethylene tube which was connected to a rapidly responding ozone analyzer. Ventilation was measured using the Respitrace (TM) inductance plethysmograph. Each subject was asked to breathe at one tidal volume during all measurements by targeting volumes which had been previously established during spontaneous resting breathing. Subjects employed three modes of breathing (oronasal, nasal, and oral) with two frequencies (12 and 24 breaths per minute [bpm]) and were exposed to three ozone concentrations (0.1, 0.2, or 0.4 ppm). Ozone removal in the supra-laryngeal airways was calculated from the concentration measured in the posterior oropharynx during inspiration and ozone removal by the lungs from the concentration measured in the posterior oropharynx during expiration. Significant, though small, differences were observed in the oronasal removal of ozone with 48.1±1.07%, 41.3±1.06% and 45.0±1.06% removed during oronasal, nasal, and mouth breathing, respectively. An average of 46.0±0.9% and 43.6±0.9% was removed at 12 and 24 bpm, respectively. Of the ozone which reached the posterior pharynx, the lungs removed 89.2±0.4% and 85.3±0.4%, respectively, at 12 and 24 bpm. While the differences in these data at each mode of breathing are probably of little physiological significance, they permit one to calculate the amount of ozone removed by the tissues and are similar to the values calculated using dosimetric models previously derived in this laboratory. It, thus, is possible to translate concentration-response curves to dose-response curves for mean changes of pulmonary function in man. This permits analysis of exposure patterns to be developed for assessment of health effects from exposure to ozone. This is a proposed presentation and does not necessarily reflect EPA policy.

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OZONE CONCENTRATION - RESPONSE RELATIONSHIP: IMPLICATIONS FOR STANDARD SETTING AND RISK ASSESSMENT. M.J. Hazucha, University of North Carolina at Chapel Hill, Center for Environmental Medicine, Medical Research Building C 224H, Chapel Hill, NC 27514

A detailed comparison of literature-reported averaged decrements in pulmonary function of normal subjects exposed to ozone has been undertaken. The data base was formed by including data published during the past 20 years, from studies which reported at least one of the pulmonary function variables (FVC, FEV_1, FEF_{25-75}, RAW), acquired at 2 hours of exposures utilizing either original or modified Bates-Hazucha (intermittent exercise) protocol, and satisfied selection criteria. The final set of data (24 studies involving 299 subjects), was divided by ventilation rate (exercise loads) into 4 categories: light, moderate, high, and very high ventilation level. For each variable (FVC, etc.) and ventilation level a quadratic function has been fitted to the data using regression procedures. The curve parameter estimates have been computed, tabulated and statistically evaluated. The slope (quadratic coefficient) for each variable within a group and almost all variables between groups were significantly different from zero and from each other at $p < 0.0001$ level. Very high regression coefficients ($r = 0.823 - 0.991$) makes the models acceptable for quantitative prediction(s) of pulmonary function decrement(s). Furthermore, the analyses show that neither "effective rate" (the product of minute ventilation and O_3 concentration), nor "effective dose" (the product of O_3 concentration, minute ventilation and exposure time) are valid concepts. Although individual studies, because of their inherent design limitations, might appear to support the validity of such calculations, a comprehensive evaluation of all data available does not confirm it. Further, a critical appraisal of the data base and derived models does not provide any convincing argument for the presence of a threshold, i.e. an O_3 concentration below which no (measurable) pulmonary function change occurs in group studies. Less reactive individuals might not show a measurable response below a certain exposure level, which could be interpreted as a threshold; however, the cummulative data best fit a continuous model. The introduction of a threshold into the tested models did not improve the fit, further supporting the arguments against the evidence of a relative threshold.

SHORT-TERM EXPOSURE EFFECT RELATIONSHIPS FOR OZONE: INFLUENCE OF CONCENTRATION, EXPOSURE TIME PER DAY AND DURATION OF EXPOSURE - P.J.A.Rombout, L.van Bree, J.A.M.A.Dormans, M.Marra and S.H.Heisterkamp, National Institute of Public Health and Environmental Hygiene, Department of Inhalation Toxicology, 3720 BA Bilthoven, The Netherlands.

A large discrepancy exists between the actual conditions of population exposure to ozone and the clinical exposures upon which health standards for ozone are mainly based. Actual ozone exposures to 80% of the maximum 1 h value may last 10-12 h per day for several consecutive days or weeks. Clinical studies typically use exposure times of ozone to three hours.
To investigate the possible health consequences of this discrepancy, rats were exposed to ozone under carefully controlled conditions to determine the relative influence of concentration, exposure time per day and exposure duration. The factors under scrutiny were quantitatively evaluated by increases in pulmonary antioxidant enzyme activities and bronchoalveolar protein accumulation. In addition, pulmonary morphological alterations were qualitatively evaluated. Exposure-response relationships were established for ozone concentrations of 150-1000 $\mu g/m^3$, exposure times of 2-24 h per day and exposure durations of 1-16 days.
Both concentration and exposure time per day had a very significant positive influence on the ozone-induced response whereas the contribution of exposure duration was only about half of that of exposure time.
Typically, ozone concentrations of 2-300 $\mu g/m^3$ caused significant biochemical and morphological alterations after continuous exposure for several days. Similar pulmonary alterations were observed after an 8 h exposure for the same duration to 800 $\mu g/m^3$.
In view of an adequate ozone health risk assessment these results support the need for clinical exposures with longer than usual exposure times and -durations. Moreover, these data favour the introduction of an additional lower ozone standard with a longer averaging time (e.g. 8 h) and/or an appropriate reduction of the present 1 h standards.

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PULMONARY FUNCTION TESTS IN THE RISK ASSESSMENT OF THE EFFECTS OF AMBIENT OZONE: AN ADVERSE HEALTH EFFECT OR A NEUROMEDIATED REFLECTORIC RESPONSE? - J. J. Vostal, General Motors Research Laboratories, Warren, MI, U.S.A.

A growing body of experimental evidence documents that respiratory airways and lung parenchyma are the targets for injury due to high concentrations of ozone. Minimal changes in pulmonary function only are produced by low ambient concentrations (≤ 0.3 ppm) of ozone that are not detected by epidemiology or animal experiments and can be observed solely in controlled human exposures. Minor decreases in peak respiratory flow rates, reported in children during summer camp activities, suffer from large variability of individual measurements. In view of significant confounding factors, such as clima or learning effects (Lioy et al., 1985), the field studies remain unconvincing. In addition, the forced expiratory volume decrements found after 0.2 ppm ozone in controlled human exposures do not represent on the average more than 4-5% of the 1-sec exspiratory volume (FEV_1) even after the heaviest exercise (U.S. EPA, 1986). The physiological significance of these changes is uncertain since both the narrowing of the airways as well as the inhibition of maximal inspiration, whether voluntary (due to discomfort) or involuntary (due to reflex pathways), are mediated by neural stimulation rather than by a direct effect of ozone on the sensitive respiratory airways. Pretreatment with atropine prevents an increase in airways resistance and partially blocks a decrease in FEV_1 (Beckett et al., 1985). The observed decrement in pulmonary function tests must be, therefore, interpreted as a transient stimulation of the airways' vagal receptors which does not have the character of an adverse health effect and cannot serve as a scientific basis for meaningful air quality regulations. Inter-individual differences in the sensitivity of nervous receptors also explain why some fraction of tested subjects ("responders") show greater than 10% reduction in FEV_1 after exposures to 0.12 ozone (McDonnell et al., 1983) and oppose the assumption that the responders represent a specific population subgroup. Recent animal experiments support the negative findings at near-ambient ozone levels since no permanent changes occur after continuous long-term exposures unless the concentrations are as high as 0.6-0.7 ppm (Gross and White, 1985, Wright et al., 1986); i.e. levels nearly twice as high as the highest reported ambient ozone concentrations.

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Datum, Unterschrift 9. Apr. 87

Exposure to MMMF in the indoor non-occupational environment - G.R. Lundqvist, Institute of Hygiene, Universitetsparken Bygning 180, DK-8000 Aarhus C, Denmark

The presence of man-made mineral fibres (MMMF) in the indoor non-occupational environment has been connected with the occurence of acute discomfort and complaints in particular from the eyes, the mucous membranes and the skin. In addition it has been debated, wheather a possible long-term risk may be associated with inhalation of even small quantities of respirable fibres.

It has in a recent field study been shown, that the number of children present and their activities during the day in a day-care institution with mineral wool slabs, is of dicisive significance for the mineral fibre content of the indoor air compared to the basic condition during the night hours. In addition it appeared, that variations could be registered from day to day and to the time spend on surface cleaning routines in the institution.

However the number of fibres released from the ceiling surface material made of compressed mineral fibres was less than 1:100 to 1:1000 of the TLV for occupational exposure, and only a small fraction of the total dust and Suspended Particulate Matter.

Testing of MMMF-slabs for release of fibres in a climate chamber and exposure models based on experimental data will be described.

MINERAL PARTICLES IN THE LUNGS OF SUBJECTS RESIDENT IN URBAN AREA - L. Paoletti et al., Istituto Superiore di Sanità, Viale Regina Elena, 299 - 00161 Rome, Italy

We started to investigate the airborne mineral particulate to which a population resident in an urban area is exposed.

This was done by studying the mineral content in lung parenchyma autoptic samples of a group of subjects having lived in an urban area but not having been professionally exposed to dusts. Much importance has been attached to obtaining data on the exposure of the population to asbestos fibers in an urban area and to assessing the type and magnitude of the possible sources of such a pollutant (motor-vehicle traffic, consumer products, etc.) by studying the fiber mineral types.

In the samples studied, up to date a total of seventeen mineral types were identified along with sixteen metal elements in the form of oxides and sulfides.

The frequent observation of tremolite fibers, an amphibolic asbestos type, was remarkable.

It is expected that the collection of a population sample as established by the selection protocol (about 200 subjects), will be completed by 1987.

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INFLUENCE OF XENOBIOTICS ON THE TOXICOKINETICS OF TOLUENE IN MAN - M. Wallén, National Board of Occupational Safety and Health, S-171 84 Solna, SWEDEN

Xenobiotics can be expected to influence the toxicokinetics of inhaled, occupationally used, solvents in man. In a series of experimental exposure studies the toxicokinetics of toluene were investigated (1) in coexposure to inhaled p-xylene, (2) in coexposure to simultaneous oral intake of ethanol, (3) in occupationally solvent exposed volunteers, (4) in painters with subjective susceptibility to solvent exposure, and (5) in connection with cigarette smoking.

(1) A mutual decrease in the blood/end-exhaled air concentration ratio was found for toluene and p-xylene when given in combination compared with separate exposure.
(2) The effects of ethanol were a decrease in the total and relative uptake as well as the apparent clearance of toluene and an increase in the toluene concentration in the blood. The solubility of toluene in blood was increased following coexposure to ethanol.
(3) After long term occupational exposure no effects on the uptake and disposition of toluene were seen in painters as compared to a non preexposed group.
(4) When the painters were subdivided into groups with and without high subjective susceptibility to solvent exposure, no differences were observed in the toxicokinetic parameters studied.
(5) Smokers were found to have a smaller elimination rate of toluene after giving up smoking than during their smoking period. The decrease in the apparent clearance was dependent on a smaller total uptake without a corresponding decrease in the blood concentration of toluene.

The toxic effects caused by toluene do not seem to be more adverse by the coexposures with the exception of the acute intake of ethanol. However, altered toxicokinetics of toluene caused by p-xylene or similar compounds or by personal habits such as moking, moderate chronic intake of ethanol, dietary factors, intake of drugs etc have to be considered especially in the case of biological monitoring and risk assessment.

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THEORETICAL DEVELOPMENT OF MECHANISM OF CHEMICAL CARCINOGENESIS------ DI-REGION THEORY - Qianhuan Dai, Center for Chemistry and Bioengineering of Cancer, Beijing Polytechnic University, East Suburb, Beijing, People's Republic of China, 100022.

In China, since 1979 a new conception named Di-region theory related to quantitative structure-carcinogenic activity relationship(QSCAR) and mechanism of chemical carcinogenesis(MCC) has been put forward[1][2], and which has got much encouragement from the international scientific cycles[3]. Based upon a new artificial intelligence strategy of quantum chemical calculation named wholesale molecular orbital calculation(WMO), which is different from the molecule by molecule calculation manner of tradition molecular orbital theory, can obtain all the parameters of a whole compound class, it is discovered that the necessary condition for the carcinogenic activity of polycyclic aromatic hydrocarbons(PAH) is the producing of two reactive centers in its metabolic course, and the favourable distance between both centers approaches characteristically to 2.80-3.00Å, which is just matching with the distance between the pair-wise negative atoms in DNA complementary base pair. Hence the key step of chemical carcinogenesis should be the covalent crosslinking between the DNA complementary base pair, and the mechanism might be the complementary frameshift along the DNA double helix. Based upon the Di-region theory conception and numerous molecular orbital parameters calculated by WMO, by using extrathermodynamics method and/or pattern recognition statistics, QSCAR of parent PAH(49), nonalternant PAH(11) alkyl PAH(187), amino-PAH(65), aza PAH(30), azo dyes(20) and N-nitroso compounds(153),have been established successfully in this laboratory. As yet, all the well-known theories related to carcinogenic mechanism including Pullman's K-region theory, Jerina's Bay-region theory as well as Miller's electrophilic theory all hold monoalkylation viewpoint, and all are faced with difculties for the establishment of QSCAR. It is surprisely that the specific bifunctional conception of Di-region theory make the puzzling QSCAR of most carcinogen series to become the graspable structure-chemical reactivity relationships. Now, the Di-region theory is being evidenced by metabolic research and other facts, and would be useful for the research on inhalation toxicology. References: [1] Dai Qianhuan,Scientia Sinica(1979),964;English edition(1980),453.[2] Dai Qianhuan,in "Polynuclear Aromatic Hydrocarbons",Cooke et al ed.,1984,p 1045.[3] cf.ES & T, (1984)3, 92A.

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